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**BULLETIN OF THE UNIVERSITY OF WISCONSIN**  
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**A CENTURY OF THE UNITED STATES  
PHARMACOPOEIA, 1820-1920**

**I—THE GALENICAL OLEORESINS**

**BY**

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**THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY  
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ABBREVIATIONS USED FOR THE TITLES OF PHARMACOPOEIAS AND  
TREATISES ON PHARMACY.

- Allg. P.—Strump, *Allgemeine Pharmakopöe*.
- Argent. P.—Argentine Pharmacopœia — *Farmacopœa Nacional Argentina*.
- Aust. P.—Austrian Pharmacopœia — *Pharmacopœa Austriaca*.
- Bad. P.—Baden Pharmacopœia — *Pharmacopœa Badensis*.
- Belg. P.—Belgian Pharmacopœia — *Pharmacopœa Belgica*.
- Bern. P.—Bernese Pharmacopœia — *Pharmacopœa Bernensis*.
- B. P.—*British Pharmacopœa*.
- B. P. C.—*British Pharmaceutical Codex*.
- Comp. to the U. S. P.—*Companion to the United States Pharmacopœia*.
- Dan. P.—Danish Pharmacopœia — *Pharmacopœa Danica*.
- Dan. Mil. P.—Danish Military Pharmacopœia.
- Dict. of Pharm. Sc.—Schweringer, *Dictionary of Pharmaceutical Science*.
- Fin. P.—Finnish Pharmacopœia — *Pharmacopœa Fennica*.
- Fr. P.—French Pharmacopœia — *Pharmacopœe Francaise*.
- G. P.—German Pharmacopœia — *Pharmacopœa Germanica*.
- Geiger's P.—Geiger's *Pharmacopœe*.
- Han. P.—Hannoverian Pharmacopœia — *Pharmakopœe für das Koenigreich Hannover*.
- Hess. P.—Hessian Pharmacopœia — *Pharmakopœe für das Kurfuerstenthum Hessen*.
- Hung. P.—Hungarian Pharmacopœia — *Pharmacopœa Hungarica*.
- Ital. P.—Italian Pharmacopœia — *Farmacopœa Ufficiale del Regno d'Italia*.
- Jap. P.—Japanese Pharmacopœia — *The Pharmacopœia of Japan*.
- King's Am. Disp.—King's *American Dispensatory*.
- Mex. P.—Mexican Pharmacopœia — *Pharmacopœa Mexicana*.
- Nat. Stand. Disp.—*National Standard Dispensatory*.
- Neth. P.—Netherlands Pharmacopœia — *Pharmacopœa Nederlandica—Nederlandische Apotheek*.
- Nor. P.—Norwegian Pharmacopœia — *Pharmacopœa Norvegica*.

- Port. P. — Portuguese Pharmacopœia — *Pharmacopœa Portuguesa.*
- Pruss. P. — Prussian Pharmacopœia — *Pharmacopœa Borussia.*
- Roum. P. — Roumanian Pharmacopœia — *Pharmacopœa Romana.*
- Russ. P. — Russian Pharmacopœia — *Pharmacopœa Russica.*
- Schlesw. Holt. P. — Schleswig-Holstein Pharmacopœia — *Pharmakopœe für Schleswig und Holstein.*
- Sp. P. — Spanish Pharmacopœia — *Farmacopœa Oficial Española.*
- Swed. P. — Swedish Pharmacopœia — *Pharmacopœa Suecica.*
- Swiss P. — Swiss Pharmacopœia — *Pharmacopœa Helvetica.*
- U. S. Disp. — *United States Dispensatory.*
- U. S. P. — *United States Pharmacopœia.*
- Univ. P. — Hirsch, *Universal-Pharmacopœe.*
- Ver. P. der Lond., Edinb. und Dub. Med. Coll. — *Vereinigte Pharmacopœen der Londoner, Edinburger, und Dubliner Medicinæ Collegien.*

## PART I — GENERAL

### HISTORICAL INTRODUCTION

The type of galenical preparation now known as an oleoresin has been official in the *United States Pharmacopoeia* since 1850, the oleoresins of cubeb and pepper being the first members of this class of preparations to receive recognition, however, under the title of fluid extract.

The suggestion for the name oleoresin appears to have come from Buchner though first applied as the name of a galenical by Peschier. The latter, in 1825, had prepared an ethereal extract of male fern which he designated *Huile de Fougère Mâle*. To this name, Buchner objected, suggesting the title *Extractum resinosum*. In reporting Peschier's work, however, Buchner speaks of the constituents of the ethereal extract as the *oelharzige Bestandtheile* of male fern, and later in his account, he refers to the finished preparation as the *oelharziges Extract*, i. e. an oleoresinous extract. It would appear, therefore, that when Peschier, in his second account (1828), speaks of an *oléorésine*, our English oleoresin, he evidently took his suggestion from Buchner's use of the German attribute, *oelharzig*.

The suggestion of Buchner, that the above mentioned preparation of male fern be called an extract, appears to have met with general favor throughout Europe as is indicated by its title in the various European pharmacopoeias, past and present. Likewise, such other members of this class of preparations as have received recognition in the European countries are to be found in the respective pharmacopoeias of these countries under the heading, *extracta*. In the United States, a latinized form of Peschier's title, *oléorésine*, has been adopted and these preparations are officially known as *oleorsinae*.

The following table of titles will give a fair idea of the early development of the synonymy of these preparations:



Table I. *Early titles of oleoresins*

1825. *Huile de Fougère Môle* — Peschier.  
 1826. *Extractum Filicis maris resinolum* — Buchner.  
 1827. *Extractum oleo-resinosum Filicis* — Brandes.  
     *Oleum Filicis Maris* — Van Dyk.  
     *Oleo-Resina Filicis*, Peschier — Ver. P. d. Lond., Edinb. and Dub.  
     Med. Coll.  
 1828. *Oléorésine de Fougère Môle* — Peschier.  
     *Extrait oléorésineux de Cubebe* — Dublanc.  
 1829. *Extractum Filicis aethereum* — App. to Pruss. P.  
     *Aetherisches Farnkrautextract* — App. to Pruss. P.  
 1832. *Extractum Filicis oleo-resinosum* — Jourdan, Univ. P.  
 1834. *Piperoide du Gingembre* — Béral.  
 1841. *Extractum Radicis Filicis Maris aethereum* — Bad. P.  
     *Aetherisches Farnkrautwurzel Extract* — Bad. P.  
     *Extractum Cubebarum aethereum* — Bad. P.  
     *Aetherisches Cubeben Extract* — Bad. P.  
 1845. *Extractum Filicis Maris aethereum* — Geiger's P.  
     *Farnwurzelextract* — Geiger's P.  
     *Extrait éthéré de Cubebe* — Geiger's P.  
     *Oleoresinous Extract of Cubebs* — Bell  
     *Ethereal Extract of Cubebs* — Procter.  
 1849. *Oleoresinous Ethereal Extracts* — Procter.  
 1852. *Extractum Filicis Maris aethereum* — Swiss P.  
     *Extrait oléo-résineux de Fougère* — Swiss P.  
     *Huile de Fougère de Peschier* — Swiss P.  
 1854. *Extractum Stipitum Aspidii* — Nor. P.  
 1857. *Oléo-Résineux de Cubebe* — Garot and Schaeuffele.  
 1859. *Oleoresina (ae)* — Procter.  
 1863. *Oleoresina Capsici* — U. S. P.  
     *Oleoresina Cubebae* — U. S. P.  
     *Oleoresina Lupulinae* — U. S. P.  
     *Oleoresina Piperis* — U. S. P.  
     *Oleoresina Zingiberis* — U. S. P.

As becomes apparent from the preceding table, oleoresins became a recognized class of galenical preparations with their introduction into the *United States Pharmacopœia* of 1860. The name, as applied to a class of galenicals, appears to have been suggested by Procter in 1846. Although this term thereby acquired a dual meaning,<sup>1</sup> it was not only shorter, but in other respects more convenient than *extracta aetherea*, previously in use in some of the European pharmacopœias. The disadvan-

<sup>1</sup> As a class of natural plant products and as a class of galenicals.

tage accruing from the substitution of *oleoresina* for *extracta aetherea* lay in the fact that as a sub-class they were removed from the other sub-classes of extracts: *e. g.*, the *extracta (solida)*, *extracta fluida*, etc. With the substitution of acetone for ether as an extracting medium, in the eighth revision of the *United States Pharmacopæia*, it is possibly fortunate that the designation *extracta aetherea* never gained a footing in this country.

The preparation of this particular class of galenicals was dependent upon the use of ether. Although, a number of chemists before the eighteenth century had obtained some ether as an ingredient of a mixture resulting from the action of sulphuric acid upon alcohol, it appears that the first commercial ether was prepared in 1730 by Frobenius,<sup>1)</sup> who, however, kept his process a secret. The use of the distillation residues for the preparation of more ether, known to Frobenius, was emphasized by several German chemists, and caused a considerable reduction in the price of this article. Thus Cadet, in 1774, pointed out that he could sell an ounce of ether at 40 sous,<sup>2)</sup> whereas Baumé had sold it at 12 livres. But even with this reduction in price, ether does not appear to have been a common pharmaceutical commodity at that time. Thus, *e. g.*, Hermbstaedt<sup>3)</sup> in 1792, mentions ether and enumerates its properties evidently for the reason that it is of pharmaceutical interest primarily because it is an ingredient of *Liquor anodynus mineralis Hoffmanni*. However, it should be remarked that Baumé mentioned it in 1762 as a solvent in the preparation of resin of Jalap,<sup>4)</sup> and in 1790,<sup>5)</sup> he described its use in the preparation of ethereal tinctures.

The first positive reference concerning the use of ether as a solvent in the preparation of a galenical of the type of our present oleoresins, that appears in the literature, is to be found in Peschier's report (in 1825) on the preparation of the *Huile de Fougère Mâle*, the present oleoresin of aspidium. As a result of the almost immediate popularity of this preparation, other pharmacists were induced to experiment with ether in attempting duplicate or modify Peschier's process. However, none of the

<sup>1</sup> Kopp. Geschicht. d. Chem., vol. 4, p. 302.

<sup>2</sup> Ibid.

<sup>3</sup> Grundriss d. exp. Pharm., part 2, p. 161.

<sup>4</sup> Éléments de Pharm. (1872), p. 284.

<sup>5</sup> Ibid. (1790), p. 262.

early workers attempted to employ it in the extraction of other plant drugs, and it was not until 1834, when Béral again called attention to the use of ether as a solvent in his preparation of *Piperoide du Gingembre*, our present oleoresin of ginger, that its value in the extraction of oleoresinous drugs appears to have been recognized. From then on, however, its use seems to have widened rapidly as the French Pharmacopœia of 1839 contained no less than nineteen ethereal tinctures. The increase in the number of oleoresins was not as rapid as might be expected in view of the statement concerning the ethereal tinctures. Only two other members of this class of preparations made their appearance before 1850, namely, the *Extractum Cubebæ aethereum* and the *Extractum Seminis Cinae aethereum*.

Some idea of the rate at which the *Extracta aetherae*, our present oleoresins, came into existence and were given official recognition will become evident from the following:

In the Prussian Pharmacopœia of 1829, but one such preparation was official, namely,

*Extractum Filicis aethereum*.

The Baden Pharmacopœia of 1841 contained three preparations of this class, viz:

- 1.) *Extractum Radicis Filicis Maris aethereum*.
- 2.) *Extractum Cubebæ aethereum*.
- 3.) *Extractum Seminis Cinae aethereum*.

The Danish Pharmacopœia of 1850 contained two preparations of this class, viz:

- 1.) *Extractum Cubebæ aethereum*.
- 2.) *Extractum Filicis Maris aethereum*.

The third edition of the *United States Pharmacopœia*, which appeared in 1851, included two fluid extracts prepared with ether as a menstrum, viz:

- 1.) *Extractum Cubebæ fluidum*.
- 2.) *Extractum Piperis fluidum*.

The Belgian Pharmacopœia of 1854 recognized no less than seven ethereal extracts, viz:

- 1) *Extrait éthéré de Fougère*
- 2) *Extrait éthéré de Cantharides*
- 3) *Extrait éthéré de Croton*
- 4) *Extrait éthéré de Cubèbe*
- 5) *Extrait éthéré de d'Aunee*
- 6) *Extrait éthéré de Bois garu*
- 7) *Extrait éthéré de Semen-contra*

It will be seen from the above array of ethereal extracts official in European pharmacopœias that the introduction of oleoresins into the fifth edition of the *United States Pharmacopœia*, which appeared in 1863, was well prepared.

Procter is commonly given credit for having introduced oleoresins into American materia medica. That he was instrumental in bringing them to the attention of the representatives of the regular medical school, and that he obtained a place for them in the *United States Pharmacopœia*, possibly no one has reason to doubt. A review of the early American literature on this subject not only reveals this fact, but it also brings out the fact that Procter appears to have been ignorant in large part of the use of this class of preparations in Europe,<sup>1</sup>) for nowhere does he mention it. It is note-worthy that it was a medical practitioner (Goddard) who first drew Procter's attention (1846), not to a typical representative of this class, but to the preparation of Dublanc which was a representative of the *extracta oleoresina* made by a very cumbersome process, now long discarded as being as unscientific as it is impractical. In the same year, the English pharmacist, Bell, had his attention drawn to this same preparation by Vore, thus showing that valuable preparations not advertised were ignored, while a quasi scientific preparation heralded about apparently attracted general attention.

To what extent the Eclectic school of medical practioners contributed to the popularization of this class of galenicals before 1860 cannot be definitely stated from the scanty informa-

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<sup>1</sup>That Procter did know of Mohr's work on this class of preparations becomes apparent when the fact is recalled that he adapted Redwood's translation of Mohr's *Pharmaceutische Technik* to American pharmacy under the title of Mohr, Redwood & Procter's *Pharmacy* in 1849, and that he had previously reviewed Redwood's translation in the *Am. Jour. of Pharm.*

tion at hand. However, it is interesting to note that the *American Dispensatory* of 1854, gives the formula of Robinson for preparing the *ethereal oil of xanthoxylum*, the present Eclectic oleoresin of xanthoxylum. The same is directed to be prepared by extracting the bark with ether and subsequently removing the ether by evaporation—a process similar to the one now employed in preparing the official oleoresins. Of but slightly lesser interest is the advertisement of Wm. S. Merrel which appeared in the *Eclectic Medical Journal* in 1855. Under the heading, Class II.—Soft resinoids and oleo-resins, etc., the following preparations were listed:

<i>Apocynin</i>	(from Dogsbane).
<i>Asclepedin</i>	(from Pleurisy Root).
<i>Aletrin</i>	(from Star Root).
<i>Eupurpurin</i>	(from Queen of the Meadow).
<i>Iridin</i> <sup>1</sup>	(from Blue Flag).
<i>Ptelein, or Oil of Ptelea</i>	(from Water Ash).
<i>Oil of Lobelia</i>	(from Lobelia Seed).
<i>Oil of Xanthoxylum</i>	(from Prickley Ash).
<i>Oil of Capsicum</i>	(from African Cayenne).
<i>Oil of Stillingia</i>	
<i>Oil of Male Fern</i>	

In view of the fact that these preparations were already being manufactured and advertised commercially in 1855, there can be but little doubt that the Pharmacopoeial Revision Committee of 1860 must have been aware of their existence and have been influenced to some extent thereby.

#### DEFINITION

Oleoresins, as a class of galencials, are extracts prepared, as a rule, with the aid of a highly selective solvent. Ether is the solvent usually employed for this purpose at the present time, whereas, acetone was directed to be used in the eighth revised edition of the *United States Pharmacopœia*. Other solvents of this nature, namely: petroleum ether, benzene, chloroform, carbon tetrachloride, et cetera, have been used, but have not been officially recognized. The oleoresin of cubeb is an exception

<sup>1</sup> Prof. John King is said to have prepared and used *Irisin* (identical with *Iridin*) in 1844. Letter from J. U. Lloyd to Edward Kremers (1906).

to the rule as alcohol is the menstruum directed to be used in its preparation.

These preparations derive their name from the fact that the drugs from which they were originally prepared contained appreciable amounts of fatty or volatile oil and resin, substances, for which ether and acetone were recognized to be good solvents. They do not by any means necessarily correspond to the so-called natural oleoresins, which consist for the main part of volatile oil and resin; but, in some cases, are products relatively poor in one or both of these constituents. Thus, for example, the oleoresin of capsicum contains little or no volatile oil and only a small amount of resin, while the oleoresin of parsley is practically free from resin. Furthermore, these preparations are not always liquid as is generally stated. The oleoresin of lupulin, for instance, is of the consistence of a soft extract when prepared according to pharmacopoeial directions, and tends to become firmer with age owing to the transformation of the so-called soft into hard resin.

The manner in which the oleoresins have been defined in the various text books and treatises on pharmacy is brought out by the following examples, which are representative of the periods corresponding to the different decennial revisions of the *United States Pharmacopoeia*:

“*Oleoresinae* — Their peculiarity is that they consist of principles which when extracted by means of ether, retain a liquid or semi-liquid state upon the evaporation of the menstruum, and at the same time have the property of self-preservation, differing in this respect from the fluid extracts which require the presence of alcohol to prevent decomposition. They consist chiefly, as their name implies, of oil, whether fixed or volatile, holding resin and sometimes other active matter in solution.” *U. S. Disp.* (1870), p. 1315.

“*Oleoresinae*, Oleoresins — Mixtures of volatile oils with resins prepared by exhausting certain drugs containing both together, the menstruum being usually ether which extracts both. The menstruum or solvent is evaporated off, and the usually semi-liquid extract which remains constitutes the oleo-resin.” Oldberg and Wall, *Comp. to the U. S. P.* (1884), p. 721.

“The oleoresins are official liquid preparations, consisting principally of natural oils and resins extracted from vegetable substances by percolation with ethylic ether. The oleoresins were formerly classed with the fluid extracts, but they differ essentially from the latter:

1. They do not bear any uniform relation to the drug as fluid extracts do, of gramme to cubic centimeter,—the yield of oleoresin obtained

from the drug varying according to the proportion of oil and resin naturally present:

2. The menstruum used, ethylic ether, extracts principles which are often insoluble in alcohol or diluted alcohol, and vice versa. Oleoresin of Cubebs, for instance, is not identical with Fluid Extract of Cubebs:

3. They are without exception the most concentrated liquid preparations of the drugs that are produced." Remington, *Pract. of Pharm.* (1894), p. 433.

"Oleoresins are those substances obtained from vegetable medicines by means of ether (sometimes alcohol, etc.,) which consist principally of a fixed or volatile oil and a resin. In some cases the resin will be held in solution by the oil, while in other cases, it will be precipitated upon standing and will require agitation to diffuse and suspend it in the oil. A third case occurs in which the oil and resin form a more or less permanent mixture, having the consistency of a very soft extract." King's *Am. Disp.* (1900), p. 1330.

"Oleoresins are ethereal extracts of an oleoresinous nature, obtained from vegetable drugs by percolation with ether." Coblentz's *Handbook of Pharm.* (1902), p. 290.

"Oleoresins, *Oleoresinae* (Oleoresins, L. *oleum*, oil and *resina*, resin)—Natural solutions of resin in volatile oils, extracted by ether, acetone or alcohol." Culbreth, *Mat. Med.* (1906), p. 20.

"The pharmaceutical oleoresins are liquid preparations of drugs containing volatile oil and resin, obtained by percolation of such drug with acetone, ether, or alcohol, and subsequent distillation of the solvent from the dissolved oleoresins." Arny, *Prin. of Pharm.* (1909), p. 259.

"Solutions of this class represent the medicinal virtues of the drugs from which they are made, in a more concentrated form than is possible in any other. They possess the power of self-preservation, and in this respect are superior to fluidextracts. Oleoresins consist chiefly of fixed or volatile oils associated with resin and other constituents; those officially recognized, with one exception, are all prepared," et cetera. Caspari, *Treat. on Pharm.* (1916). p. 354.

## DRUGS USED, THEIR COLLECTION, PRESERVATION, ETC.

Since the oleoresins are characterized chiefly by their content of oil and resin (see definition above), it is evident that they may be prepared from many of the numerous vegetable drugs) of which these substances constitute an appreciable part. The number of such drugs, however, which has actually been used for this purpose, is comparatively small as is shown in the table which follows. The table also reveals the fact that nearly all of these drugs are derived from phenogamous plants and that they consist, as a rule, of those organs in which oils and resins are usually present in the greatest abundance.

TABLE 2—*Drugs from which oleoresins have been prepared.*

<i>Phenogams</i>		
Alkanet (root)	Cypripedium (rhizome)	Pepo (seed)
Anacardium (fruit)	Eucalyptus (leaf)	Pepper (fruit)
Annatto (seed)	Galangal (rhizome)	Pomegranate (root)
Asarum (root)	Ginger (rhizome)	Ptelea (bark)
Capsicum (fruit)	Helenium (flower)	Pyrethrum (root)
Cardamon (seed)	Iris (rhizome)	Sabal (fruit)
Chenopodium (fruit)	Kousso (flower)	Santonica (unexp. flower)
Clove (unexp. flower)	Lobelia (seed)	Savine (leaf)
Conium (leaf)	Lupulin (strobile)	Senecio (root & herb)
Croton (seed)	Matico (leaf)	Spiraea (herb)
Cubeb (fruit)	Mezereum (bark)	Taxus (leaves)
	Parsley (fruit)	Xanthoxylum (bark)

*Cryptogams*

Aspidium (rhizome)	Ergot (sclerotium of <i>Claviceps purpurea</i> )
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Of the total number of drugs enumerated above, seven have been utilized in the preparation of the oleoresins official in the *United States Pharmacopoeia*, namely:

Aspidium	Ginger	Parsley
Capsicum	Lupulin	Pepper
Cubeb		

With respect to the collection (harvesting) of the foregoing and their preparation for use, there is little of a general nature to be said as the plants from which these drugs are obtained differ so widely in their habits. This subject will, therefore, not be given consideration here, but will be discussed in Part II under the treatment of the individual preparations.

## SOLVENTS USED.

At the present time, ether is the solvent directed to be employed in the preparation of the official oleoresins with the exception of the oleoresin of cubeb which is prepared with alcohol. It will be recalled that the first of this class of preparations to make its appearance, namely, the *Huile de Fougère* of Peschier, was also prepared with ether. In fact, ether appears to have been the only solvent<sup>2)</sup> given consideration in this connection by the early European investigators.

<sup>1</sup> One animal drug, cantharides, has been utilized for the preparation of an ethereal extract. This preparation, which was official in the Belgian *Pharmacopoeia* of 1854, cannot properly be classed with the oleoresins since it contained no resin—the animal organism being free from constituents of this nature.

<sup>2</sup> Buchner in 1826 experimented with alcohol in preparing the *Extractum Filicis resinosum*, while Brandes, in 1827, made use of a menstrum containing both alcohol and ether, namely the *Liquor anodynus*, for the same purpose. Later, 1828, Dublanc and Oberdoerffer employed alcohol in the preparation of the oleoresinous extract of cubeb.



With the introduction of the oleoresins into the *United States Pharmacopæia* of 1860, and their extensive use in this country, a number of American pharmacists were lead to the conducting of experiments, which had for their main object the discovery of a solvent less expensive and less dangerous to handle than ether. We must, however, note that prior to this time (1860) an attempt was made by Berjot, a Frenchman, to use carbon disulphide for the purpose of preparing the *Extrait oléo-résineux de Cubebe*. Garot and Schaeuffele, in 1857, in a paper on Berjot's preparation showed that nothing was gained by its use, as two and one-half times as much carbon disulphide as ether was required to extract the drug. Furthermore, the removal of the last traces of this solvent was a matter of considerable difficulty.

The solvent which first appears to have suggested itself to American investigators was benzin as is indicated in the publications of Procter, Maish, Trimble and others. The first account of its use in this connection appeared in 1866, when Procter published his results on the preparation of the oleoresin of cubeb. The following table shows the relative value of alcohol, benzin and ether for the extraction of cubeb as found by Procter.

TABLE 3.—Yield of oleoresin of cubeb.

Quantity of drug	Menstruum	Total Yield
grains		grains
1000.....	Alcohol .....	250
1000.....	Benzin.....	170
1000.....	Ether.....	219

While Procter could find no objection to the use of alcohol as a solvent in the preparation of this oleoresin, he advised against the use of benzin as he stated that it did not extract the cubebin completely.

Simultaneously with the above publication of Procter, there appeared an account of a general method for preparing the oleoresins by Rittenhouse. The latter also worked with benzin, but employed it as a "follow up" solvent after percolation had been partially completed with ether. He also experimented with glycerin and fusel oil, employing them in a similar manner.

In 1872 Maish published a review of the experiments of A. H.

Bolton and M. Roth. The latter of these two men conducted an investigation on the extraction of ginger and cubebs with benzin, the former also included capsicum in his series of experiments. These workers found that ether still extracted some non-volatile matter after the drugs had presumably been exhausted with benzin. Further, that, while the benzin oleoresins were all soluble in ether, the ethereal oleoresins of cubeb and ginger were only partially soluble in benzin, thus confirming Procter's work in 1866 on the oleoresin of cubeb.

Henry Trimble was the next investigator<sup>1</sup>) to experiment to any considerable extent with benzin as a solvent. In his report to the Pennsylvania Pharmaceutical Association, in 1888, on commercial oleoresins, he stated that while benzin was in his opinion preferable to concentrated ether for the extraction of capsicum, it would not answer for the other official oleoresins. Following is a table showing the comparative extractive powers of ether and benzin as compiled by Trimble:

TABLE 4—*Relative extractive power of benzin and ether.*

Drug	Yield with ether	Yield with benzin
	Per cent.	Per cent.
Aspidium .....	6.51	5.1
Capsicum .....	19.5	18.15
Cubeb .....	21.26	16.65
Lupulin .....	60.59	7.04
Pepper .....	8.79	2.80
Ginger .....	3.97	2.48

Results similar to the above with respect to the oleoresins of ginger were reported by Samuel J. Riegel in 1891.

About this time George M. Beringer became interested in the preparation of the oleoresins, and in 1892, he published an account of his researches, in which he had employed not only ether and benzin as extracting menstrua, but also the heretofore little used solvent, acetone. With respect to benzin, he arrived at the same conclusions as did Trimble, *viz*: that its use

<sup>1</sup> In 1877, L. Wolff in an article entitled: *The use of Petroleum Benzine in Pharmacy*, stated that benzin extracted none of the pungent resin from ginger, no cubebic acid from cubeb, no piperin from pepper and no santolin or resin from wormseed.

is not permissible in the preparation of the official oleoresins<sup>1</sup>), except, perhaps in the case of capsicum, and then only under certain restrictions, namely: that percolation be terminated after 2 cubic centimeters of percolate are obtained for every gram of the drug, as upon further percolation, the oleoresin becomes almost solid owing to the large increase of palmitin extracted. In his experiments with acetone<sup>2</sup>) he found that, as with ether, the first portion of the percolate contained nearly all the medicinal ingredients of the drug. He, however, continued percolation until the drug was exhausted. The marc was then removed from the percolator, dried and re-percolated with stronger ether; but except in the case of capsicum no further extractive matter was obtained. The oleoresins were stated to be of excellent quality and the yield and properties were nearly the same as when ether was used. He especially recommended the use of acetone in preparing the oleoresin of ginger, as he claimed that it was in every way equal to the preparation made with ether. Following is a table showing Beringer's results with acetone as compared with ether and benzin:

TABLE 5—Relative extractive values of acetone, ether and benzin.

Drug	Yield to acetone		Yield to ether		Yield to benzin	
	U. S. P. method	Complete exhaustion	U. S. P. method	Complete exhaustion	U. S. P. method	Complete exhaustion
	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
Aspidium.....		18.00			16.18	
Capsicum.....	18.00 <sup>1</sup>	25.00	17.32		21.00 <sup>1</sup>	25.00
Cubeb.....		25.00				
Cubeb.....		24.10				
Cubeb.....		21.75				
Ginger.....		5.57				
Lupulin.....		71.00		70.80		
Parsley.....		24.00 <sup>2</sup>				22.30
Pepper.....		5.93 to 9.97 <sup>3</sup>		5.00 to 6.70		

<sup>1</sup> Two cubic centimeters of percolate were collected for each gram of drug.

<sup>2</sup> Represents total extract from which 3 per cent. of wax precipitated, leaving 21.00 per cent. of oleoresin.

<sup>3</sup> Represents total extract which yielded 5.93 per cent. of oleoresin.

<sup>1</sup> Pile (1867) confirms this statement in so far as it concerns the oleoresin of ginger. He states that neither benzin nor ether completely extract ginger, but that alcohol is the best solvent for this purpose.

<sup>2</sup> The acetone used by Beringer was procured from manufacturers of chloroform as the product obtained from the distillation of wood was found to consist largely of methyl alcohol and even higher boiling fractions.

From a comparison of the above data with those obtained by Trimble (See table 4), it would appear that acetone is equally as serviceable as ether in the preparation of the official oleoresins. Such appears, also, to have been the opinion of the Revision Committee of the United States Pharmacopœia of 1900, as the edition, which became official in 1905, directed that acetone be employed in the manufacture of those oleoresins which were formerly required to be prepared with ether.<sup>1</sup> That this change was unsatisfactory is evidenced by the numerous comments on the subject occurring in the literature, and by the fact that ether is again directed to be used for this purpose in the ninth revised edition of the *United States Pharmacopœia*.

To those unacquainted with the situation, the above action of the Revision Committee of 1910, might be taken to indicate that the matter of the proper solvent to be employed in the manufacture of these preparations has been definitely settled and the superiority of ether in this respect firmly established. A close inspection of the preceding reports, along with other information of a similar nature occurring in the literature, would, however, appear to point out, that, as in the case of the oleoresin of cubeb, other solvents might be advantageously employed in the preparation of certain of these individuals. In this connection the use of benzin,<sup>2</sup>) or better, petroleum ether,<sup>3</sup>) in the preparation of the oleoresins of capsicum and parsley fruit might be mentioned, or the employment of acetone in the preparation of the oleoresin of ginger.<sup>4</sup>) As further evidence of the possibilities along this line, attention is also called to the experiments of Wollenweber (1906) on the extraction of aspidium with benzene, and to the mention of chloroform<sup>5</sup>) and carbon tetrachloride<sup>6</sup>) as solvents for the preparation of the oleoresins in general.

The manner in which these solvents have been employed in

<sup>1</sup>The most important factor in determining this change was probably the difference in cost of the two solvents at the time (1900), acetone being the cheaper. This statement is confirmed in a measure by the fact that now, since the price of ether has been reduced, owing to its preparation from denatured alcohol, it is again the solvent officially recognized.

<sup>2</sup>See preceding reports by Trimble, Beringer and others.

<sup>3</sup>Hyers (1895) also made use of petroleum ether in extracting cubeb.

<sup>4</sup>Idris (1898) stated that he found acetone, b. p. 65° C, to be the most suitable solvent for extracting ginger.

<sup>5</sup>Dorvault, *L'Officine* (1898), p. 591.

<sup>6</sup>Lucas, *Practical Pharmacy* (1908), p. 149.

the preparation of the various oleoresins will be discussed in a general way under methods of preparation and in detail under individual oleoresins.

### METHODS OF PREPARATION

The methods of preparing the oleoresins as outlined in the present edition of the *United States Pharmacopœia* may be stated in the following general way: extract the drug completely<sup>1</sup> by percolation, expose the percolate in a warm place until the solvent has completely evaporated and separate the remaining liquid portion from any deposited material. This is essentially the method of procedure given in most of the late editions of the foreign pharmacopœias as well, notable exceptions being the German and Japanese. In the two latter, the drug is directed to be exhausted by maceration instead of percolation. In detail, the methods described in the United States Pharmacopœia, as well as the foreign pharmacopœias, differ somewhat with the particular oleoresin as will be brought out to some extent in the following discussion and more minutely under the separate treatment of each individual. It is perhaps needless to state that these methods are not of recent invention but have been gradually evolved from the numerous experiments conducted both in this country and abroad.

The first of these experiments dates back to the year 1825, when Peschier prepared the *Huile de Fougère Mâle*, our present oleoresin of aspidium. In his description of the method of preparation, he directs that the male fern rhizomes be extracted with successive portions of ether, the decanted ethereal solutions mixed and evaporated at a gentle heat, and the remaining oily residue collected and preserved as the finished product. This is essentially the method which appeared in the early European pharmacopœias as is shown in the following typical example taken from the Prussian Pharmacopœia of 1830:

Agitate one ounce of powdered male fern root with successive portions of eight ounces of ether until the ether decants clear. Then mix the several portions and strain. Distill down to one-fourth of the volume and evaporate the remainder on a water bath to a thin yellowish-brown extract.

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<sup>1</sup> Percolation, in the extraction of capsicum is directed to be discontinued when eight hundred mills of percolate have been obtained.

An inspection of the above method brings out the fact that the decanted menstruum was directed to be clarified by the process of straining. Not only was a great deal of the solvent lost by evaporation in this procedure, but a very considerable amount remained adhering to the marc. While some of the latter was, in actual practice, removed by pressing the drug on the strainer with the hands, Mohr<sup>1</sup>) in commenting on the method stated that, inasmuch as three-fourths of the ether were often lost in these operations, it was useless to recover the remainder by evaporation. To overcome this loss to some extent, he suggested making these preparations in the winter when the low temperature would be less favorable for the volatilization of the solvent. As ether, at this time and for many years later, was a comparatively expensive solvent, it will become apparent that a change in the method was to be desired.

The first decided departure<sup>2</sup> from the above method of procedure, which appears to have been given official recognition, is to be noticed in the Baden Pharmacopœia of 1841. The method briefly stated is as follows:

Mix the powdered male fern root with a sufficient quantity of ether to thoroughly moisten it. Then extract it in a *Real'sche Presse* so connected with a receiving flask that none of the menstruum will be lost by evaporation.

A few years later, in 1846, there appeared a method in the Swedish Pharmacopœia which likewise included the process of displacement, viz:

Macerate the male fern root, cut in small pieces, with ether and extract in a displacement apparatus.<sup>3</sup> Then distill the ethereal solution to one-fourth of its volume and evaporate the remainder on a water bath to the consistence of a thin extract.

Even with the use of a pressure percolator, so much ether was still lost through spontaneous evaporation and through ab-

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<sup>1</sup> Mohr, Redwood and Procter's *Pharmacy* (1849), p. 263.

<sup>2</sup> Geiger, in 1827, employed the *Real'sche Presse* in the preparation of the *Oleum Filicis Maris*, our present oleoresin of aspidium.

<sup>3</sup> The apparatus employed for this purpose was most probably the *Filtre-press* of Count Real or the *Luft-press* of Dr. Romershausen, as both of these so-called presses were in general use at that time. In fact, both are mentioned in connection with the preparation of the *extracta* by the Prussian Pharmacopœia as early as 1834.

sorption by the bag,<sup>1</sup>) that, in operating with small quantities of the drug, the recovery of the remainder was scarcely worth the trouble. The recognition of these defects by Mohr lead him to construct (in 1847) a special form of apparatus for continuous extraction with volatile solvents. However, while Mohr's apparatus was a success from an economical standpoint, there is no evidence to show that it was ever employed to any extent by the American pharmacist, although, Procter, the American editor of Redwood's translation of Mohr's treatise on pharmacy, advocated its use in this connection in 1849.

About this time (1846) Procter caused the American pharmacists to become interested in this class of preparations by calling attention to his improvement upon Soubeiran's method (as suggested by Dublanc)<sup>2</sup>) for preparing the *Extrait oléo-résineux de Cubebe*, a preparation similar to our present oleoresin of cubeb. The following is the method as devised by Procter.

"Take cubebs, in powder, one pound avoirdupois, and sulphuric ether a sufficient quantity, which is two and one-half to three pounds; introduce the powder into a displacer, insert the lower end into a bottle that fits it, add the ether carefully, and cover the top of the filter with a piece of wet bladder through which several pin holes have been made." The flow should be very gradual and if too rapid, the filter should be partially closed with a cork. By attention to this point, much less ether will be required. The ethereal tincture should be introduced into a large retort, heated by a water bath, and the receiver well refrigerated. The distillation should not be hurried toward the last. When five-sixths of the ether have passed, it should be separated for use, and the evaporation be continued in the retort, observing to keep the temperature below 120°F, so as not to volatilize the volatile oil."

A few years later (1850), this method (in essential detail) was given recognition by the *United States Pharmacopœia* in connection with the preparation of the fluid extracts of cubeb and pepper, later known as the oleoresins of cubeb and pepper, respectively. For the purpose of better bringing out this

<sup>1</sup> Mohr, Redwood and Procter's *Pharmacy* (1849), p. 268.

<sup>2</sup> Although Dublanc described a method for preparing the oleoresinous extract of cubeb, similar to that of Soubeiran, in 1828, neither method is given consideration here as both differed to such an extent from the usual procedure that they had little or no influence on the development of the present process.

<sup>3</sup> From the above description, it appears that the form of displacer used by Procter was the one described in Mohr, Redwood and Procter's *Pharmacy*, (1849), p. 270.

similarity, the following general statement of the pharmacopœial methods is also given :

Take of the Drug, in powder, a pound;

Ether a sufficient quantity.

Put the drug into a percolator, and having packed it carefully, pour the ether gradually upon it until two pints of filtered liquid are obtained, then distill off by means of a water-bath, at a gentle heat, a pint and a half of the ether, and expose the residue in a shallow vessel, until the whole of the ether has evaporated.

The methods in general as they were given in the *United States Pharmacopœia* of 1860 differ from the above only in the quantity of drug and menstruum directed to be taken. Thus, twelve troy ounces of drug were directed to be subjected to percolation with ether until twenty-four fluidounces of filtered liquid were obtained, when eighteen fluidounces of the ether were to be removed by distillation. In the preparation of the oleoresin of ginger, however, the following method of procedure was given :

“Take of Ginger, in fine powder, twelve troyounces;

“Stronger ether twelve fluidounces;

“Alcohol a sufficient quantity.

“Put the ginger into a cylindrical percolator, press it firmly, and pour upon it the stronger ether. When this has been absorbed by the powder, add alcohol until twelve fluidounces of filtered liquid have passed. Recover from this, by distillation on a water-bath, nine fluid-ounces of ether, and expose the residue in a capsule until the volatile part has evaporated.”

That the Pharmacopœial Revision Committee was informed of the work of Béral in this connection appears to be clearly evident, as it was he, who first suggested this procedure (1834), also, in the preparation of the oleoresin of ginger, then known as the *Piperoïde du Gingembre*.

In 1866, Rittenhouse, commenting on the methods in general, which were given in the *United States Pharmacopœia* of 1860, stated that about thirty-six fluid ounces of ether were required to extract the drug when proceeding as officially directed. He, however, conceived the idea of reducing the amount of ether by a procedure similar to that employed in extracting the ginger rhizomes. Alcohol did not appeal to him as the proper “follow up” solvent for this purpose and he, therefore, conducted a series of experiments, in which he made use of benzin,



glycerin and fusel oil. The following is the working formula finally devised by him:

“Take any convenient quantity of the drug; for each ounce thus employed,  $1\frac{1}{2}$  fluid ounces of ether, and 1 fluid ounce or q. s. of benzin. Pack the drug in a suitable apparatus, add the ether, and when it has ceased to pass, pour on the benzin in the proportion of one fluid ounce for each ounce of the drug employed or until as much percolate has been obtained as equals the amount of ether employed. Recover the ether by distillation in the usual manner.”

The process of Rittenhouse does not appear to have received much attention as there is no subsequent mention of it to be found in the literature.

During the meantime Procter continued his work on the oleoresins and in the same year (1866), he pointed out that practically all of the oleoresinous material was to be found in the first portions of the percolate, and that a considerable quantity of menstruum could be saved by discontinuing the operation before the drug was completely exhausted. The following table compiled by Procter clearly brings out this point:

TABLE 6—Yield of oleoresin of cubeb to ether, alcohol and benzin.

Quantity of cubeb	Solvent	Quantity of 1st percolate	Yield of oleoresin	Quantity of 2nd percolate	Yield of oleoresin	Total yield
grains 1000 “ “	Ether Alcohol Benzin	grains 1000 “ “	grains 205 240 140	grains 1000 “ 2000	grains 14 30 25	grains 219 250 170

The effect of Procter's work is noticed in the 1870 and 1880 editions of the *United States Pharmacopœia*. Thus, the Pharmacopœia of 1870 directed that twenty instead of twenty-four fluidounces (as formerly required) of percolate be collected for every twelve troyounces of drug, while the Pharmacopœia of 1880 required that only 150 parts of percolate be obtained for every 100 parts of drug taken. It should also be noted, that in the 1880 edition, the method of preparing the oleoresin of ginger was made to conform with that given for the other oleoresins.

The *United States Pharmacopæia* of 1890, directed, that, in the preparation of all of the official oleoresins, the drug be completely exhausted by percolation with ether. The following directions for the preparation of the oleoresin of cubeb are typical of the methods given:

“Cubeb, in No. 30 powder, 500 Gm.; ether a sufficient quantity.

“Put the cubeb into a cylindrical glass percolator provided with a stop-cock, and arranged with a cover and receptacle suitable for volatile liquids. Press the drug firmly and percolate slowly with ether, added in successive portions, until the drug is exhausted. Recover the greater part of the ether, etc.”

The next edition of the *United States Pharmacopæia* (1900) contained a number of changes with respect to the methods of preparing this class of galenicals. Two new solvents were introduced, namely, acetone and alcohol; the method of procedure was modified in the case of the oleoresin of capsicum, and an ordinary percolator was directed to be used in the preparation of the oleoresin of cubeb. The following is a general statement of the manner in which the oleoresins of aspidium, ginger, lupulin and pepper were directed to be extracted.

Introduce the powdered drug (degree of fineness specified) into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and receptacle suitable for volatile liquids. Pack the powder firmly, and percolate slowly with acetone, added in successive portions, until the drug is exhausted.

The method of extracting the cubeb was stated as follows:

Introduce the powdered cubeb (degree of fineness specified) into a cylindrical glass percolator, pack the powder firmly, and percolate slowly with alcohol, added in successive portions, until the cubeb is exhausted.

The method described for the extraction of capsicum was similar in all respects to the first of the methods given above, except that percolation was directed to be discontinued when eight hundred cubic centimeters of percolate had been obtained.

The above changes, except in the case of the oleoresin of cubeb<sup>1</sup>) must be attributed to the work of Beringer, an account of which was published in 1892. Not only did he advocate the use of acetone in these preparations, but he also pointed out

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<sup>1</sup> It will be recalled that Procter in 1866 suggested the use of alcohol in preparing the oleoresin of cubeb. See table 3, page 922.

the advantage of discontinuing percolation short of exhaustion in the case of capsicum.

The ninth revised edition of the *United States Pharmacopæia* shows but one change in the method of preparing the oleoresins, viz: ether is directed to be used in those cases where acetone was employed in the preceding edition.

From the foregoing discussion, it becomes apparent that the *United States Pharmacopæia*, even to the present edition, has consistently adhered to the process of simple percolation in extracting the oleoresinous drugs. This condition not only appears strange, in view of the fact that modern methods of operating with the volatile solvents, such as ether, make use of some form of continuous extraction apparatus; but is thought to show a lack of progress as well. Maish, in 1900, suggested the use of Soxhlet's apparatus for this purpose and pointed out its advantage, especially when operating with small quantities of drug. Reference is also made in this connection to similar forms of apparatus in most of the present day text-books on pharmacy.

With reference to the preparation of the oleoresins on a commercial scale, there is good reason to doubt the employment of any of the heretofore mentioned methods. The method most likely in use at the present time is one similar to that official in the *British Pharmacopæia* of 1867. The latter, briefly stated, is as follows:

Exhaust the powdered drug by percolation with alcohol, and distill the percolate until a soft extract is obtained. Treat this extract with successive portions of ether, mix the ethereal solutions and again distill off the solvent, when the residue will constitute the oleoresin.

The advantage of this method lies in the fact that it requires the handling of comparatively small amounts of ether, and thereby lessens the danger incurred in working with large quantities of this highly inflammable solvent. The disadvantage is that alcohol may not extract all of the ether-soluble material from the drug.

In the preceding survey, only the official oleoresins and their methods of preparation have been considered. There is, however, a number of preparations which have been classed as oleoresin, in Parrish's *Treatise on Pharmacy*, and King's *American Dispensatory*, although, they have never received of-

ficial recognition. They are the so-called Eclectic oleoresins and are in general directed to be prepared in the following manner:

Extract the drug by percolation with alcohol or ether and precipitate the oil and resin by pouring the alcoholic or ethereal tincture into water. Lastly, separate the product from the water by filtration.

Among the preparations which have been made in this way are the following: oleoresin of iris (iridin), oleoresin of xanthoxylum, oleoresin of cardamon (oil of cardamon), oleoresin of ergot, (oil of ergot) and oleoresin of parsley,<sup>1</sup> (oil of parsley).

In this connection, it should be pointed out that the foregoing are liquid preparations and do not constitute the so-called resinoids, which are solids, although prepared in a similar way.

#### APPARATUS EMPLOYED.

Under the two preceding headlines, the preparation of the oleoresins has been discussed from the standpoint of the solvent employed in extracting the drug, and with respect to the method of procedure. There, is however, still another factor of interest which deserves consideration in this connection, namely: the form of apparatus made use of.

It will be recalled that the first of this class of preparations to make its appearance, the oleoresin of aspidium, as originally prepared, required the use of nothing but a macerating jar, a cloth strainer and some sort of container, in which the colated liquid could be collected and exposed to the air to permit the evaporation of the solvent. Likewise, these were the utensils generally employed in the experimental stages of the preparation of the other members of this class which became known at an early date. As soon, however, as the oleoresins became recognized as regular pharmaceutical commodities, the method of preparation as outlined above was found to be impractical owing to the complete loss of the solvent by evaporation. In adapting the same to commercial use, steps were, therefore, taken to recover as much of the latter as possible. For this purpose, some form of distilling apparatus was employed, pre-

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<sup>1</sup> This preparation should not be confused with the oleoresin of parsley as official in the present edition of the *United States Pharmacopæia*.

sumably, the retort and condenser. Even with this modification, however, a large part of the solvent was still lost in the operation of straining.

About this time (1820 to 1840), the extraction of drugs by the process of downward displacement was attracting considerable attention, and, as the pharmacist saw in this procedure a means of eliminating the operation of straining, it is not at all surprising that it should have received early application in the preparation of the oleoresins. In explanation of the method of procedure as followed at the time, it should be stated that it was in reality a process of percolation under pressure, and, as such, required the use of a special form of apparatus. Two such forms were already available at the time when the oleoresins became a subject for investigation, namely: the *Filtre-Pressé* of Réal and the *Luft-Pressé* of Romershausen. In fact, Geiger made use of the former in the preparation of the oleoresin of male fern as early as 1827. While these forms of pressure percolators eliminated the process of straining, their use, nevertheless, appears to have been disadvantageous in certain other respects. For instance, the method of operation was rather cumbersome, and a considerable amount of solvent was absorbed by the cloth bag containing the powdered drug, thus rendering the apparatus of little value in working with small quantities of the latter.

As a result of the early work with the pressure percolators, experimentation along this line was stimulated and it was soon shown that drugs could be completely extracted by simple percolation under ordinary atmospheric pressures. The first evidence of the use of a simple percolator in the preparation of the oleoresins appears in Béal's account of his preparation of the *Piperoïde du Gingembre* in 1834. Fifteen years later (1849), Procter, in an article on the oleoresinous ethereal extracts, mentioned two forms of simple percolators, a conical percolator made of tin, and Gilbertson's displacement apparatus constructed of glass. Both of these were similar in essential detail to the percolators in general use at the present time. In fact, the *United States Pharmacopæia* still directs that these preparations be made by simple percolation, a modified form of Gilbertson's displacement apparatus being specified for use in this connection. This condition seems strange, indeed, in view of the fact that modern methods of operating with volatile

solvents, such as ether, make use of some form of continuous extraction apparatus.

Such an apparatus was invented by Mohr in 1847 and its advantages in the preparation of the oleoresins pointed out by him at this time, and later, by Procter. An apparatus operating on similar principles was described by Parrish in 1884 in his *Treatise on Pharmacy*. More recently Maish (1900) has suggested the use of the Soxhlet apparatus for the preparation of small quantities of oleoresins, while a number of other forms of continuous extraction apparatus have been mentioned in this connection in the various periodicals and text-books on pharmacy.

The different forms of apparatus, which have been mentioned at various times in connection with the preparations of the oleoresins, and the methods of operating with the same are described in detail in the following chronological list:

Cadet, C. L.

Filtre-presse de M. Réal.

Jour. de Pharm., 2, pp. 165 and 192; Repert. der Pharm. 2, p. 356.

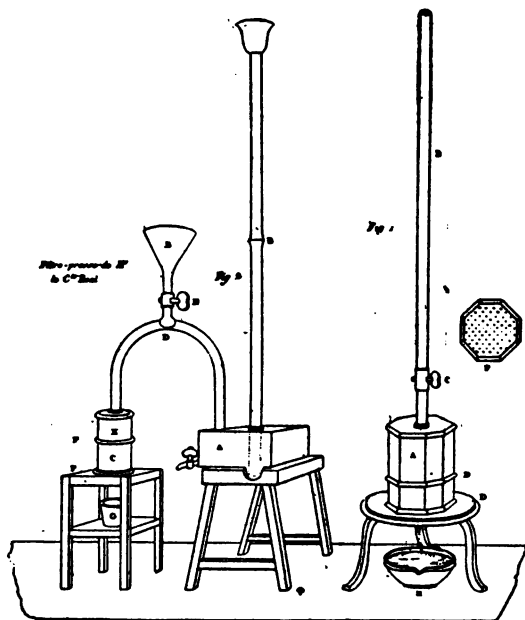


Fig. 1.) The body of the extraction apparatus A is made of tin, the top of which, being screwed on, can be removed. It is

supported on a tripod. At D and D' are two false bottoms between which the material to be extracted is packed. Into the cover of the apparatus, the pipe B, which may be 50 to 60 feet high, is fitted. The communication between B and A may be stopped by means of the stop cock C. The dish E under the tripod receives the percolate.

Fig. 2.) The second figure is a modification of the first doing away with the long tube. The solvent is admitted to the space X by pouring it into the funnel E. The percolate is collected in the container G. The pressure is secured by filling the cast iron container A with mercury. After the apparatus C is charged with drug and solvent, the stop-cock H is closed and the pipe B also filled with mercury which then forces the menstruum through the firmly packed drug.

Buchner, J. A.

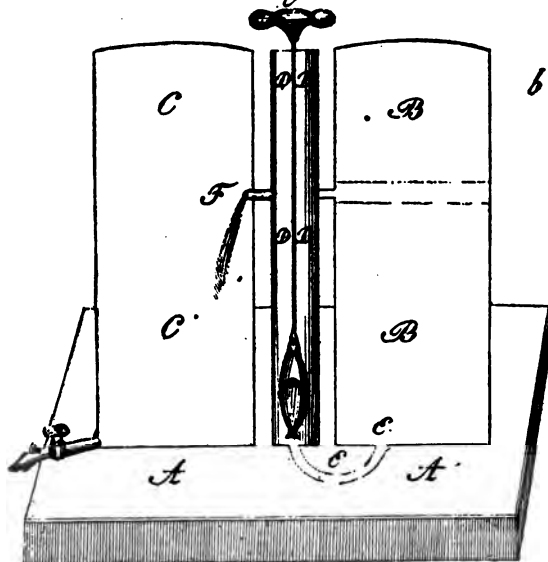
1819

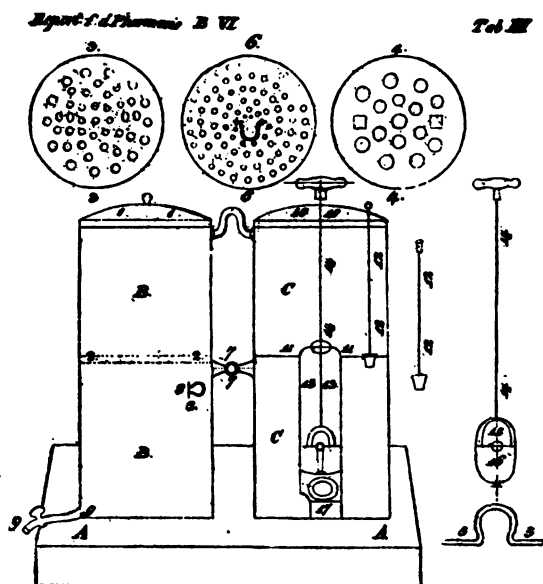
Beschreibung und Abbildung der von Herrn Dr. Romershausen erfundenen Luft-presse.

Repert. der Pharm., 6, p. 316.

*Repert. f. d. Pharmacie B. VI*

*Fig 2*





The two twin cylinders B and C are mounted on the support A and are provided with covers 1 and 10. On the support, the diaphragm 3 is placed, covered with a straining cloth which is held in position by the diaphragm 4 which in turn is fastened by the clamp 5. A third diaphragm 6 is used to cover the substance to be extracted. The two cylinders are united by the tube 7 provided with a stop-cock. The lower part of B is also provided with a stop-cock, at S in order to allow the percolate to flow out at 9. The lower section of C is converted into an air tight compartment by the cover 11, which is provided with an opening and stopper at 12. The parts indicated by 13, 14, 15, 16, and 17 belong to the suction pump necessary to create a vacuum. The suction pump is outside the cylinder and the percolate is not allowed to collect underneath the percolator B, but is at once pumped in the reservoir C.

Beindorff

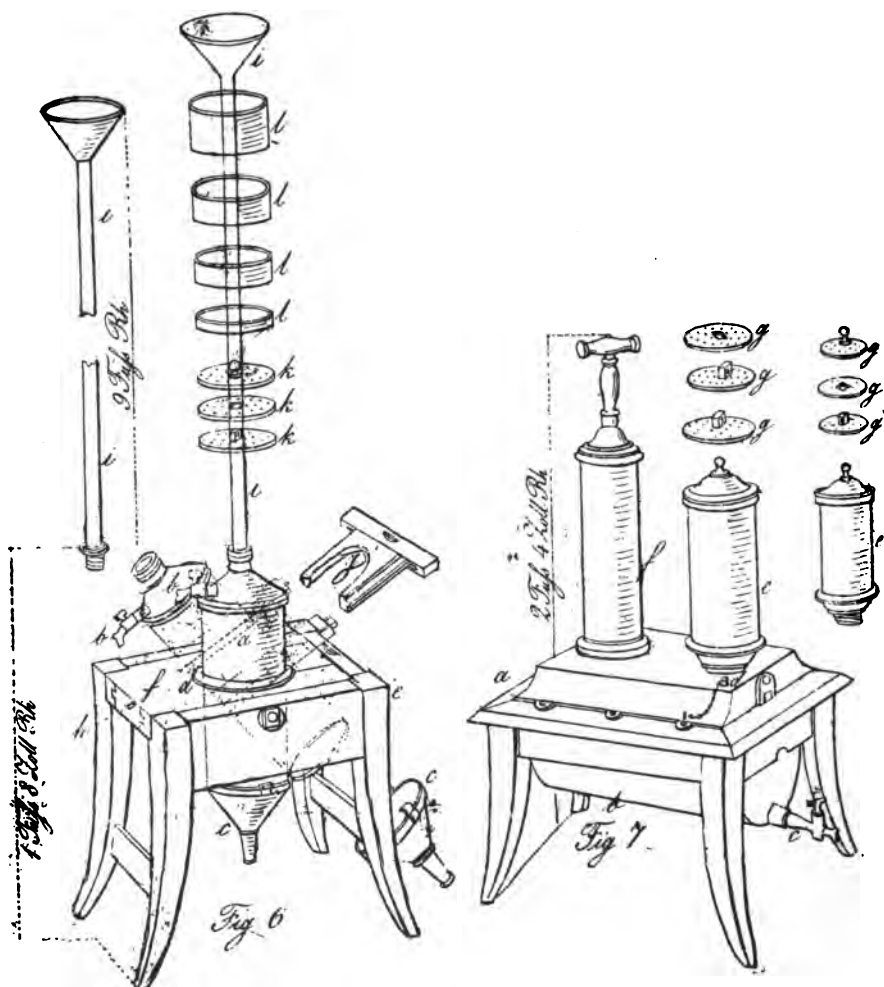
1826

Mag. f. d. Pharm., 9, p. 185. [Geiger, Hanbuch d. Pharm. (1830), p. 142].

The cuts represent Beindorff's modification of the Réal and Romershausen extraction apparatus. It will be noticed that the apparatus in figure 6 is so mounted that it can be tipped



at a convenient angle for filling and emptying. In figure 7, a more compact form of the apparatus is shown. In the latter, the long tube is replaced by an air pump.

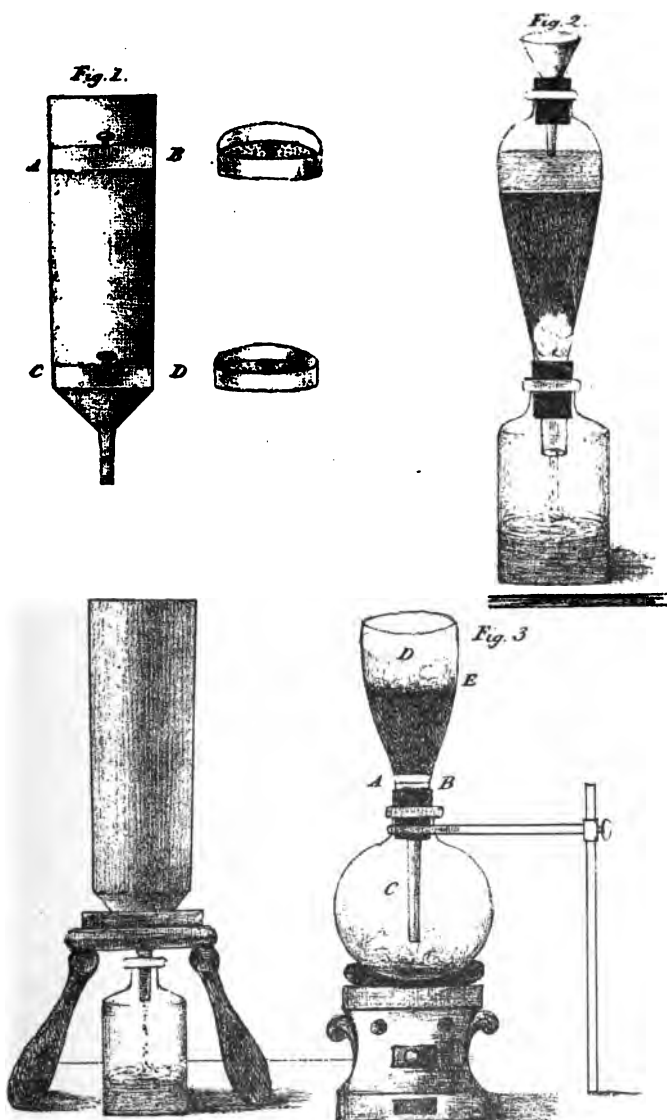


These forms of pressure percolators were mentioned in connection with the preparation of the oleoresins by Mohr (1854) in his *Commentary on the Prussian Pharmacopoeia*.

Simonin

1834

Journ. de Pharm. et de Chim., 20, p. 128.

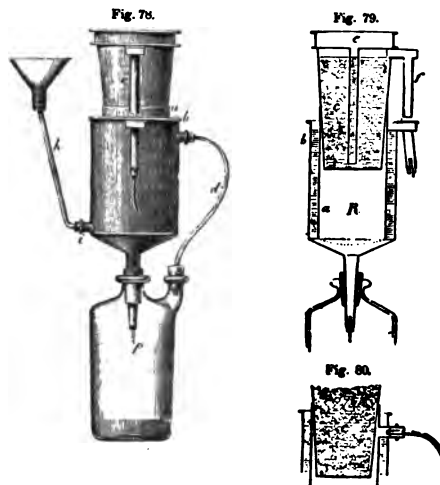


It is thought that one of the above represents the form of percolator made use of by Béral (1834) in his preparation of the *Piperoide due Gingembre*.

Mohr

1847

Neuer Extractions Apparat fuer Weingeist und Aether.  
Arch. der Pharm., 100, p. 305. [Am. Journ. Pharm., 21,  
p. 117].



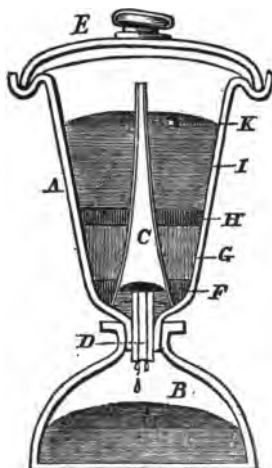
The apparatus consists of a two-necked Woulf's bottle, figure 78 p, into the central mouth of which the metallic vessel R, figure 79, is fitted by means of a cork. The vessel R consists of a metallic cylinder *a* having a perforated strainer *k* near the bottom and terminating with a funnel neck, to admit of its being fitted into the Woulf's bottle. This cylinder is surrounded by a second cylinder *b*, the space between them being intended to contain either hot or cold water. In the top of the inner cylinder *a*, a slightly conical vessel *c* is made to fit air tight, as shown in the drawing. This vessel *c* is intended to be used as a condensing apparatus, and for this purpose it is filled with cold water. From the second or lateral opening of the Woulf's bottle, a glass or tin tube *d*, figure 78, is carried to the upper part of the cylinder *a*, where it is inserted as shown in figure 80. The cold water in the vessel *c* is renewed through the pipe *e* which conducts it to the bottom, while the warm water runs off from the top through the pipe *f*, figure 79. Hot or cold water is renewed to the space between the two cylinders R by the tube funnel *h*, figure 78, and the water from this space overflows into *g* and is carried off together with that from *f*. The tube *h* is inserted through a perforated cork at *i* so that by turning the

tube downwards, the water from the space between the cylinders can be run off.

1849

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Mohr, Redwood and Procter's Pharmacy, p. 270.



This consists of a conical vessel A with a water joint rim at the top into which the cover fits. A tube D is ground to fit into the opening in the bottom, and over the end of this tube is placed a conical tube C, the lower end of which has several notches cut in it, so that the liquid can pass under when placed as shown in the drawing. The lower extremity of the vessel A is ground to fit into the mouth of the receiver B.

The above apparatus was mentioned by Procter, in 1849, in his article on "the preparation of the oleoresinous ethereal extracts."

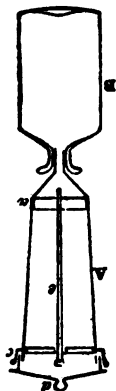
1849

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Mohr, Redwood and Procter's Pharmacy, p. 272.

A is an ordinary tin displacer, except that the rim *c* is soldered around the mouth, in such a manner as to form a water joint when the rim of the cover *d* is placed in it; *a* is a perforated diaphragm, *e* a tin tube open below and above. The latter is soldered to the lower diaphragm, through which it passes, while the upper diaphragm slips over it loosely. In using the dis-

placer, the ingredients are introduced around the tube to a suitable height, the upper diaphragm put in its place, and menstruum poured on, the joint half filled with water and the lid inserted. The atmosphere of the bottle B communicates with that of A through the tube *e*.



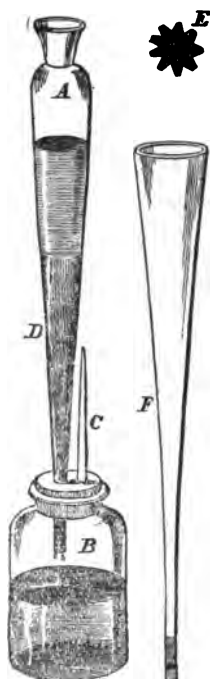
This form of percolator was mentioned by Procter (1849) in his article on "The oleoresinous ethereal extracts."

1849

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Mohr, Redwood and Procter's *Pharmacy*, p. 270.

Figure A is a glass adapter, which is selected of suitable size. The lower extremity of this is partially stopped with a cork cut as represented in F. A layer of coarsely pounded glass is put over the cork, and above this a layer of clean sand, thus forming a strainer for arresting the passage of the solid particles of material to be acted upon. The end of the adapter is fitted, by means of a perforated cork, into the mouth of the bottle. A glass tube, one end of which is drawn to a capillary opening, is also fixed in the cork as shown at C so as to allow the air to escape out of the bottle as the liquid drops in. A piece of bladder may be tied over the mouth of the vessel at A to prevent the evaporation of the solvent, but a few pin holes must be made in the bladder to admit of the ingress of air as the liquid passes into the receiver below.



The above form of percolator was mentioned by Procter (1849) in his article entitled *The Preparation of the Oleoresinous Ethereal Extracts*.

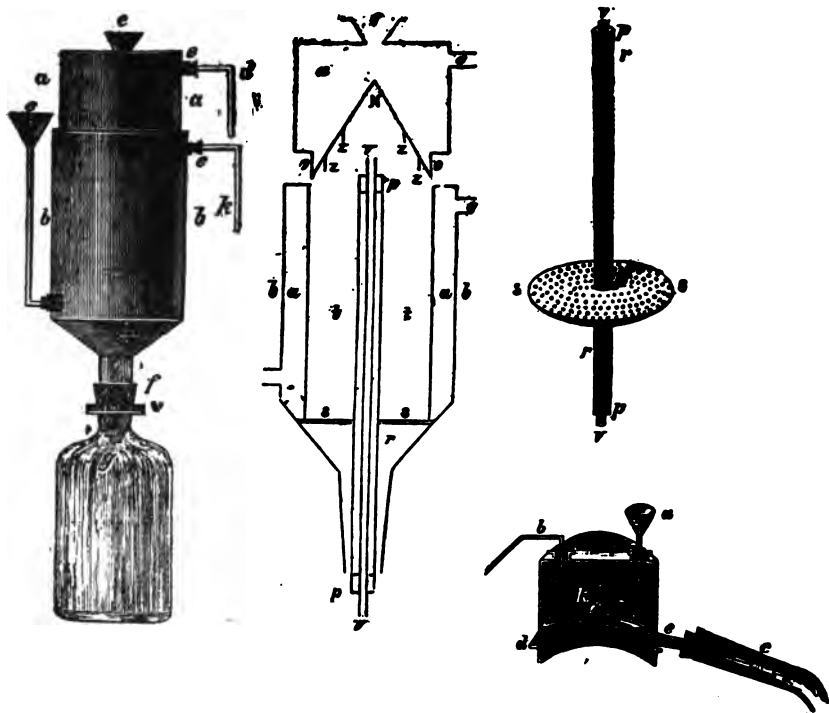
1873

Utensilien zur Bereitung der aetherischen und weingeistig-aetherischen Extracte.

Hager's *Commentar zur Pharmakopœa Germanica*, 1, p. 620.

This consists of a cylinder *bb* fitted into a cork *f* which is inserted into the neck of a flask or bottle *g*, *aa* is a cover which serves as a condenser. In the lower end of the cylinder *bb* is a tin sieve plate *ss* in the center of which is a tin tube *rr* enclosed in a glass tube *vv*. The glass tube is held firmly in place by a cork at each end *pp*. The condenser *aa* has a conical shaped bottom *N* around the interior of which run two corrugated rings *zz* of tin. The space *a*, Fig. B, contains cold water which enters from the openings *cc* and flows out through

the tubes *ee*. As soon as the menstruum drops through colorless, the top *aa* is taken off and D put on in its place. It is also a condenser. The water flows in at *a* and off through *b*. The conical bottom K is so arranged that the condensed solvent



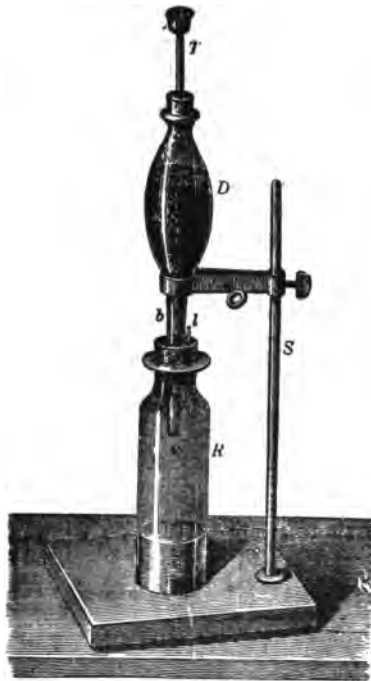
drops from off the receiver *i* and is carried off into a flask through the outlet *e*. The space between *vv* and *aa* is filled with either hot or cold water.

1873

Utensilien zur Bereitung der aetherischen und weingeistig-aetherischen Extracte.

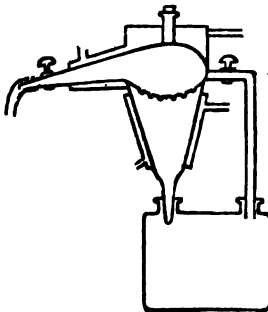
Hagers *Commentar zur Pharmakopœa Germanica*, 1, p. 622.

A displacement tube D with a wide mouth at its upper end is closed with a cork through which runs a thistle tube T. The lower end is pushed through a cork which fits tightly in a receiving bottle R. The small glass tube *l* is for the purpose of letting the air escape from the receiver R.



1884

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 Parish's *Treatise on Pharmacy*, p. 755


A percolator of tinned copper is surrounded by a jacket of the same material; the receiver is a copper vessel with two necks into one of which the percolator is secured, the other is connected with a pipe leading to the closed head of the percolator which is also jacketed; on the other side of the head is a perforated plate



of tinned copper, which distributes the ether over the surface of the drug when it has been volatilized by placing the receiver in hot water. After the exhaustion of the drug, the receiver is removed, the lower orifice of the percolator closed, and the head well refrigerated; a stream of hot water is then passed into the jacket around the percolator, by which means the contained ether may be recovered.

1886

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Remington's *Practice of Pharmacy* 1886, p. 366.

The apparatus consists of a cylindrical percolator fitted into the mouth of a receiving bottle with the aid of a cork. The upper part of the percolator being closed and a small opening left in the cork to allow the escape of air from the receiving bottle.



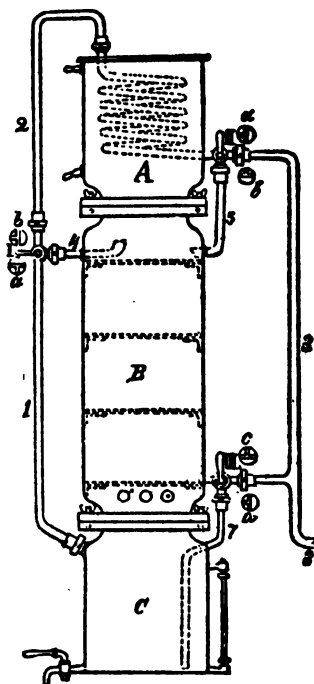
A continuous extraction apparatus can be made of this percolator by enclosing the upper part in a suitable case and passing cold water between, arranging the apparatus like a Liebig's condenser. A glass tube is connected with the top of the percolator and the mouth of the bottle by rubber tube connections,

and if the receiving bottle be placed in a water bath and the water gently heated, the ether will evaporate from the percolate, the vapors rising in the tube and condensing in the upper part of the percolator.

Lewin R.

1887

Ein neuer Extractions Apparat,  
Arch. der Pharm., 215, p. 74. [Proc. A. Ph., 35, p. 12.]



This apparatus is adapted for 1) continuous extraction with hot menstrua, 2) continuous extraction with cooled menstrua, 3) recovery of the menstrua from the finished extract by direct distillation.

It is composed of three easily separable principle parts: C, the tinned copper still, B, the copper percolator, which is provided with three movable sieve bottoms for the reception of

1) For continuous extraction with hot solvents, the vapors pass from the still C, in the tube 1, and enter through the tri-

faucet I, when in position *a*, through tube 4, into the percolator, the substance to be extracted. A is the condenser.

B, penetrate the substance to be extracted, and condense. The percolate passes into the receiver and from this flows through the tri-faucet III in its position *a*, through the tube 7, again into the still, to repeat this course as long as it may be desirable. To prevent pressure in the apparatus, the tube 2, is removed during this operation, and the tri-faucet II is placed in position *a*. This admits the vapor into the cooling worm, A, which thus forms a safety valve.

2) For the continuous extraction with cooled solvents, the vapors pass from the still C, into tube 1, and enter through the tri-faucet I, in its position *b*, through tube 2, into the cooling worm A, from this as a liquid through the tri-faucet II, in its position *a*, into the percolator, and so through the substance to be extracted into the still as before.

3) For the recovery of the solvent from the extract by direct distillation, the vapors pass from the still C, through tube 1, through the tri-faucet I, in its position *b*, through tube 2, into the cooler, A, through the tri-faucet II in its position *b*, into the exit tube 3, which latter may be lengthened at pleasure.

Portions of the percolator may be removed from the receiver at pleasure through the tri-faucet III, in its position *c*, by the tubes 2 and 3. All of the tubes are connected or disconnected by good screw joints.

Flueckiger, F. A.

1889

Ein zweckmaessiger Extraktionsapparat.

Arch. d. Pharm., 227, p. 162. [Proc. Am. Pharm. Assoc., 37, p. 338].

The extraction tube A is provided at C with a diaphragm from the center of which a small tube or neck extends into the funnel D. The tube B F attached to the side, passes into a tubulure G, which is provided with an ordinary cork K by means of which communication through the tube B F, between the upper, and the lower portions of the apparatus may be cut off or established. Thus causing the condensed liquid to return through the drug when the communication is closed or allowing the liquid to be distilled off when it is open.



Caspari in his *Treatise on Pharmacy* (1916) describes the use of this apparatus in connection with the preparation of the oleoresins.

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1890

Szombazi Soxhlet's Extraction Apparatus.

Dingler's pol. Journ., 256, p. 461. [Zeitschrift f Anal. Chem., 19, p. 365.]



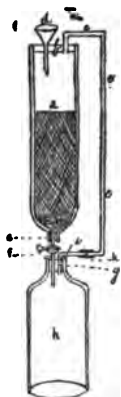
Maish (1900) first suggested the use of this apparatus in the preparation of the oleoresins.

Alpers, William C.

1896

Oleoresinae.

Merck's Rep., 5, p. 593. [Proc. Am. Pharm. Assoc., 45, p. 435.]



The apparatus consists of a cylindrical percolator *a*. The upper end of the percolator is closed with a large cork *b* through which two holes have been bored—the one for receiving a bent glass tube *c*, the other for a small glass funnel *d*. The lower narrow end of the percolator is closed by a cork *e* through which a straight connecting glass cock *f* passes into another perforated cork *g* that closes the receiving bottle *h*. This cork contains a second perforation with a small bent glass tube *i*. The glass tubes *c* and *i* are joined by means of a small piece of rubber tubing at *k*.

1902

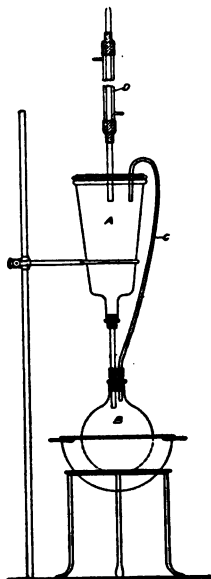
Coblentz's *Handbook of Pharmacy*, p. 290.

A is a percolator with a stop cock C. It is inserted into a receiver B. The receiver B and percolator A are connected

with a tube as shown in the figure for the purpose of equalizing the pressure as the apparatus is closed throughout.

1908

Brandel and Kremers, *Percolation*, p. 52.



A is an ordinary conical percolator of such a size that it will not be more than two-thirds filled with the drug to be extracted. B is a round-bottom flask, containing a twice perforated stopper, through one hole of which a glass tube connects the flask to the percolator. Through the second hole is inserted the glass tube C which also passes through the cork stopper in the top of the percolator. The end of the condenser D is also inserted through this cork. All cork connections should be tightly sealed with gelatine.

The above is the form of apparatus which was used in the laboratory in the preparation of the oleoresins when 500 grams or more of the drug were extracted.

## YIELD

The yield of oleoresin is a variable quantity depending, first of all, upon the oleoresin content of the particular drug from which it is prepared. Thus, the oleoresin content of ginger is only about one-half that of the aspidium and one-fourth that of cubeb. Not, only, however, does the oleoresin content vary with the different drugs, but the drug, when of the same genus and, species, may show a variation due to a number of influences, such as the climate in which grown, time of harvesting, conditions under which stored, *et cetera*. As an illustration of these influences, aspidium may be taken. The maximum yield of oleoresin, in this case, is obtained from the freshly dried Russian rhizomes collected in the month of September.<sup>1</sup>) Or, the case of ginger may be cited. In this instance, the African rhizomes harvested at maturity (usually in February)<sup>1</sup>) give the largest amount of oleoresin. This characteristic will be taken up in detail under the treatment of the individual oleoresins. The other important factors in determining the amount of oleoresin obtained, in general, are two in number, *viz*: the solvent employed in extracting the drug, and the method employed in operating with the same. Both of these factors have been dealt with in a general way under the two preceding headings. They will also be discussed more fully in connection with the individual preparations.

## CHEMISTRY

The Chemistry of the oleoresins *per se* has apparently received but little attention, except in the case of the oleoresin of aspidium. The latter has been the subject of numerous investigations and its chemistry is now understood fairly well. Some work has also been done toward determining the composition of the oleoresins of cubeb and lupulin, but our present knowledge of the chemistry of these preparations is still very indefinite.

A very considerable amount of work has been done toward clearing up the chemistry of the drugs from which the oleoresins are prepared, and it is from this source that we are

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<sup>1</sup> See tables of yield under the oleoresins of aspidium and ginger, respectively.

obliged to obtain what information we have concerning the composition of most of these preparations. It is for this reason that the chemistry of the drugs from which the oleoresins are prepared is given consideration in this monograph. See "Chemistry of the drug and its oleoresin" under the treatment of each individual oleoresin.

### PHYSICAL AND CHEMICAL PROPERTIES

The determination of the physical and chemical properties of the galenical oleoresins in general does not appear to have been undertaken systematically in the past. While there are numerous references in the literature concerning color, odor, taste and consistence, there is no mention, except in connection with the oleoresins of aspidium and cubeb, of the properties which we should naturally expect to find under a description of a class of preparations of this nature, *viz*: specific gravity, refractive index, acid number, saponification value, *et cetera*. This condition is surprising in view of the work which has been done along this line in connection with the natural products of the same name. That cognizance is, however, being taken of the subject at the present time is evidenced in the comparatively recent work which has been done abroad on the oleoresin of aspidium. In the latter case, the methods usually employed in fixing the standards of similar natural products were applied, and with considerable success. A brief general discussion of these properties as well as other characteristics, which have been mentioned in this connection, follows.

### PHYSICAL PROPERTIES

#### *Color:*

The color is a characteristic property of the individual members of this class of preparations. Considered with respect to a single member, it serves in some cases as a measure whereby the quality of the product may be roughly determined. Thus, a brown color in the oleoresin of aspidium indicates an inferior preparation, in the making of which old deteriorated rhizomes have been used, whereas, a deep green color is said to indicate adulteration with salts of copper. Likewise, a brown color in the oleoresin of cubeb warrants the opinion that ripe instead of unripe fruits have entered into its preparation. How-



ever, as the color of the individual preparations, when properly made, varies to a considerable extent, and as the description of exact shades is a difficult matter, this property as described in the literature is naturally somewhat indefinite. This subject will receive further consideration of the treatment of the individual oleoresins.

#### *Odor:*

The oleoresins without exception possess distinct odors resembling in an intensified degree those of the drugs from which they are prepared. In general, this property offers a ready means of identifying these preparations. In specific instances, it may also serve as an indication of the quality of the product. For example, a rancid odor in the case of the oleoresin of aspidium is evidence of the use of old deteriorated rhizomes in its preparation or of undue exposure to the air while kept in storage. For similar reasons, the oleoresin of lupulin may have a disagreeable cheesy odor. Furthermore, unevaporated solvent, even when present in comparatively small amounts, may be most easily detected by this means. This property will be discussed in greater detail under the individual oleoresins.

#### *Taste:*

The taste of the individual oleoresins, like the odor, is a property acquired in an intensified degree from the drugs from which they are prepared. Likewise, this property also serves as an aid in the identification of these preparations. In addition, however, it has been made the basis of a quantitative physiological test <sup>(1)</sup> for the determination of the quality of the oleoresins of capsicum and ginger. For a further discussion of this property, see the individual oleoresins.

#### *Consistence:*

The U. S. P. oleoresins, with the exception of the one prepared from lupulin, are liquids. The degree of fluidity, however, varies with the individual under consideration, with the temperature and with certain other conditions, which will be discussed in detail under the separate treatment of each individual. The oleoresin of lupulin is usually of the consistence of a very soft extract.

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<sup>1</sup> See under the oleoresins of capsicum and ginger respectively.

*Solubility:*

The solubility of the different oleoresins naturally depends to a large extent on the solvent which was employed in their preparation. It does not, however, follow from this statement that, because an oleoresin was prepared with ether, it will always be completely soluble in the same. Some of these preparations on standing undergo chemical changes with a resulting change in solubility. For example, the oleoresin of aspidium forms a deposit on ageing, and the deposited material is practically insoluble in ether. As a rule, the oleoresins, when prepared with ether, form clear or slightly cloudy solutions with absolute alcohol, acetone and chloroform, whereas, they are only partially soluble in petroleum ether and carbon tetrachloride.

In the case of certain members of this class of preparations, this property has been of considerable value in detecting adulterations or in the identification of the solvent which was employed in their manufacture. For specific instances of the application in this connection, see under the oleoresins of aspidium and ginger.

*Specific gravity:*

The value of determining the specific gravity as an aid to standardizing the oleoresins appears to have been first noted by Procter. In 1866, he published data showing how this constant, in the case of the oleoresin of cubeb, varied with the solvent employed in its preparation, and further pointed out that a low specific gravity observed in the commercial product was, in one instance at least, an indication of the incomplete removal of the solvent, ether. Procter's observations were as follows:

TABLE 7.—*The specific gravity of the oleoresin of cubeb.*

Drug	Solvent	Specific gravity	Remarks
		at 76° F.	
Cubeb.....	Alcohol.....	0.9850	Prepared by Procter.
"	Ether .....	0.9875	" " "
"	Benzin .....	0.9325	" " "
"	Ether .....	0.9000	Commercial sample containing ether.

This work, however, appears to have received but little attention as there is no further mention of the determination of this

constant in this connection in the literature until 1903. In that year, the English firm of Southall Brothers and Barclay published a statement in their *Laboratory Reports*, in which a standard range for the specific gravity of the oleoresin of aspidium was given. Interest in the matter again seems to have waned and it was not until 1911, when Parry showed that the last named preparation was being extensively adulterated with castor oil, that the necessity for standardizing this preparation became apparent. The subject was then taken up in earnest, however, and in 1913, no less than four articles on the determination of the physical and chemical constants of the oleoresin of aspidium made their appearance. In each of these, the determination of the specific gravity was given some consideration.

From the foregoing brief résumé of the literature on this subject, it becomes apparent that the determination of the specific gravity as a factor in evaluating the oleoresins has received consideration in connection with but two of the official preparations. Furthermore, that practical use has been made of this constant only in the case of the oleoresin of aspidium. The results obtained with respect to these two preparations, however, are deemed to be of sufficient importance to warrant the determination of this constant in the case of the other members of this class of preparations.

The manner in which this constant was determined by the above mentioned investigators does not become apparent from their work as reported in the literature. It is thought, however, that an ordinary glass pycnometer and chemical balance were employed for this purpose. In the determinations made in the laboratory, a 10 cubic centimeter pycnometer was used, except in the case of the oleoresin of lupulin which was usually too thick to handle in this manner. For the determination of the specific gravity of the latter, a Nicholson's hydrometer was employed. All determinations were made at 25° C.

The results as obtained in the laboratory and those reported elsewhere will be discussed in detail under the treatment of the individual oleoresins.

#### *Refractive index:*

The determination of the refractive index has received consideration only in connection with the standardization of the

oleoresin of aspidium. In this case, it has proven to be of particular value in detecting adulteration with castor oil as was first pointed out by Parry in 1911. Subsequent work by other investigators has not only confirmed Parry's observations, but has shown that in some instances a low refractive index may be an indication of a low filicin content due to natural causes<sup>1</sup>) as well.

Since most of the other official oleoresins are sufficiently transparent to permit of the direct determination of this constant, it was thought that such determination might likewise prove to be of some aid in standardizing these preparations. That such an opinion has proven to be correct will be shown in connection with the discussion of this topic under the individual cases.

For the determination of this constant in the laboratory, the Abbe refractometer was employed, all observations being made at 25° C. In those cases (the oleoresins of ginger and lupulin) where the color was too intense to permit of a direct determination being made, the oleoresin was dissolved in an equal volume of castor oil and the refractive index computed from the following formula:

$$n_D(b) = 2n_D(a + b) - n_D(a)$$

a = refractive index of castor oil.

b = " " " " oleoresin.

## CHEMICAL PROPERTIES

### *Loss on Heating:*

The oleoresins without exception lose weight on drying. This loss is usually referred to in the literature as the moisture content. It has been determined by heating the preparation at 100 to 105° C. for a definite period of time, or until of constant weight. The fallacy of designating the loss of weight thus obtained as the moisture content becomes evident when we take into consideration the fact that these preparations contain volatile substances other than water, which would also be removed by heating to a temperature of 100° C. Indeed, the oily

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<sup>1</sup>The male fern rhizomes have been shown to vary in filicin content due to the climatic conditions under which they were grown, time of harvesting, *et cetera*. See under "Drug used, its collection, preservation, *etc.*"

nature of these preparations exclude the presence of any great quantity of moisture. This statement has been borne out by laboratory experiments. Attempts to determine the moisture by means of the xylene<sup>1</sup>) method failed to reveal the presence of a measurable amount of water in any of the samples examined. The loss in weight is, therefore, due, ordinarily, to the removal of volatile oil and in exceptional cases to the removal of unevaporated solvent. Such being the case, the determination of this constant serves as a means of measuring the amount of volatile oil naturally occurring in these preparations and as a means of detecting the presence of unevaporated solvent.

The amount of weight lost by the oleoresins when determined as stated above varies greatly with the individual members comprising this class of preparations. The oleoresin of cubeb which contains a comparatively large amount of volatile oil naturally sustains a comparatively great loss, while the oleoresin of capsicum which contains a small amount of volatile matter shows but a slight loss. There is noted a further variation in the case of each individual due to a variation in the amount of volatile matter naturally occurring in the drug from which the oleoresin was obtained, or to a variation in the conditions under which the individual was prepared. As an illustration, the oleoresin of cubeb may be cited. The volatile oil content of cubeb is stated to be 10 to 18 per cent. A much greater variation is, therefore, to be expected in the oleoresin which represents only the alcohol soluble portion of the drug. With respect to the conditions under which the oleoresin of cubeb is prepared, observations in the laboratory have shown that the preparation will contain a larger amount of volatile oil when the solvent is allowed to evaporate spontaneously at room temperature, than when the same is removed by evaporation on a water bath. In most cases, the variation, due to the difference in solvent used in extracting the oleoresins, appears to be so slight as to be almost negligible. In the case of the oleoresin of pepper, however, there is a very noticeable difference. This is very likely due to the nature of the preparation, its viscosity making it difficult to remove the last traces of the less volatile solvents without the application of heat.

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<sup>1</sup> U. S. Dept. Agric., Forest Service, Circ. 134.

In the determinations of this nature made in the laboratory, a weighed amount of the oleoresin (about 2 grams) was heated in an electric oven at 100° C. for 3 hours, cooled in a desiccator and weighed, the difference in the two weights being taken as the loss.

A more detailed consideration of this subject will be found under the treatment of the individual oleoresins.

#### *Ash Content:*

The determination of the ash content of the oleoresins is of special value in identifying the solvents which have been used in their preparation. Such determinations, made in this laboratory, also by the firm of Dieterich<sup>1</sup>) in Helfenberg, have shown that, while there is as a rule comparatively little difference in the ash content of these preparations, when prepared with the same solvent, there is a marked variation in the case of each individual when different solvents are employed. The oleoresin of lupulin is an exception to this rule. Its ash content varies to a considerable extent even when prepared with the same solvent.

In addition to the above, the qualitative examination of the ash of commercial samples has revealed the fact that nearly all of them contain copper, due in most cases to the action of the free fatty acids on the utensils employed in their preparation. In some instances, the presence of the metal must be attributed to the addition of copper salts for the purpose of imparting the desired green color to preparations of inferior quality. See under the adulteration of the oleoresins of aspidium and cubeb, respectively.

The ash content of the oleoresins examined in the laboratory was determined as directed by the last edition of the *United States Pharmacopœia* under "Determination of Ash or Non-volatile Matter," p. 589.

Copper, when present, was identified by the blue color of the solution formed when the ash was dissolved in a few drops of hydrochloric acid, diluted with water, and ammonium hydroxide solution added.

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<sup>1</sup> The firm of Dieterich has for a number of years determined the ash content of the oleoresins of aspidium and cubeb. A tabulation of the results as obtained by this firm will be found under the separate treatment of these oleoresins.

For a more detailed discussion of this subject, see under individual oleoresins.

*Acid Number:*

Kremel in 1887 determined the acid numbers of the oleoresins of aspidium and cubeb. Inasmuch, however, as he made but one determination in each case, no conclusions can be drawn from his work. Similar determinations made in this laboratory on all of the official oleoresins show that this property varies greatly depending on the particular individual under consideration. Furthermore, that no general statement can be made as to its value in fixing the standards of these preparations, but that it is of importance when considered in connection with individual cases as will be brought out later.

For the manner in which this constant was determined in the laboratory, see the *United States Pharmacopœia*, ninth revision, (1916), p. 591.

*Saponification Value:*

The saponification values of the official oleoresins, as determined in this laboratory and elsewhere,<sup>1)</sup> indicate that this property may be an important factor in fixing standards for these preparations. The results obtained by Parry, Harrison and Self, and others show that in the case of the oleoresin of aspidium, the saponification value varies directly as the filicin content, and is, therefore, useful as a check on the determination of the latter. Considered in connection with such of these preparations as contain easily oxidizable substances, an abnormally high saponification value is very likely caused by an increase in the acid content due to the action of the oxygen of the air, and is thus an indication of an old product<sup>2)</sup> or of improper care in storing. As an example, the oleoresin of lupulin may be cited. In this case, a high saponification value signifies an old preparation or one that has been prepared from deteriorated drug.<sup>3)</sup> These factors, together with the influence of the solvent employed and the method of preparation on this property, will

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<sup>1</sup> Saponification values have only been determined in the past in the case of the oleoresin of aspidium and in one instance in the case of the oleoresin of cubeb.

<sup>2</sup> See oleoresin of aspidium.

<sup>3</sup> See oleoresin of lupulin.

be considered in greater detail under the treatment of the individual members.

The manner in which this constant was determined in the laboratory is described on p. 590 of the *United States Pharmacopæia*, ninth revision.

#### *Iodine value:*

The determination of the iodine value as an aid to the standardization of the oleoresins appears to have been first employed by the firm of Dieterich in Helfenberg in 1904, however, only in the case of the oleoresin of aspidium. It has since received further practical application, in connection with the same preparation, by the English firm of Evans Sons, Lescher and Webb, while a number of similar determinations have been made by the author. The results<sup>1)</sup> obtained with respect to this preparation show that the iodine value varies directly as the filicin content, and, therefore, serves as another check on the determination of the latter constituent.

With respect to the other official oleoresins, it may be stated that, as a general rule, the iodine value is high in the case of those preparations which contain a large amount of unsaturated constituents of ether fatty or volatile oil.<sup>2)</sup> Further than this, it may be influenced largely by the nature of the other constituents of these preparations and will be considered in detail in connection with the treatment of each individual.

For the method employed in the laboratory in the determination of this constant, see the *United States Pharmacopæia*, ninth revision, p. 590.

#### SPECIAL TESTS

While the different official oleoresins can, as a rule, be identified without difficulty, the use of various adulterants in their preparation, through ignorance in some cases, or with willful intent on the part of unscrupulous manufacturers, has made it necessary to guard against this practice by making use of certain qualitative and quantitative tests. As will be brought out later, such tests have been applied principally to the preparations official in foreign countries, namely: the oleoresins

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<sup>1</sup> See under oleoresin of aspidium.

<sup>2</sup> See under oleoresin of cubeb.



of aspidium and cubeb. No tests of this, or, as a matter of fact, of any kind have been included in the *United States Pharmacopœia*. It is thought, however, that if interest in these preparations could be awakened in this country, the need of similar precautions with respect to all of the official oleoresins would become apparent.

#### *Qualitative Tests:*

Inasmuch as the common physical properties, such as odor, taste and appearance, are very characteristic of the oleoresins, it is hardly necessary to resort to other means for their identification. It appears, however, that the use of the so-called false cubebs in the preparation of the oleoresin of cubeb has made necessary a more certain method of identification. Such a method, based on the red color produced when concentrated sulphuric acid is added to the oleoresin prepared from the genuine fruit,<sup>1</sup>) has, therefore, been given in most of the late European pharmacopœias. Likewise, the use of other species of fern in the preparation of the oleoresin of aspidium caused a qualitative test for this preparation to be included in the late editions of the Austrian, Hungarian and Netherlands pharmacopœias. For the details of these methods, see qualitative tests under the respective oleoresins.

#### *Quantitative Tests:*

On the whole, very little has been done in the past toward developing quantitative methods for the evaluation of the oleoresins. This condition is perhaps due, for the main part, to an imperfect knowledge of the chemistry of most of these preparations, as well as to the lack of exact information concerning the constituents of therapeutic value. In the case of the oleoresin of aspidium, however, the therapeutic value of the preparation has been shown to depend upon a number of acid constituents, the quantity present varying through natural and artificial causes. As a result, various methods<sup>2</sup>) for the determination of the total acid content have been devised and are in use at the present time, a modification of the original method of Fromme being officially recognized in the late edition of the British and Swiss

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<sup>1</sup> Dekker states that the so-called false cubebs give a yellow color with concentrated sulphuric acid. *Pharm. Ztg.* (1912), 84, p. 845.

<sup>2</sup> See under oleoresin of aspidium.

pharmacopœias. The only other work of this nature appears to have been done quite recently (1914) by the H. K. Mulford Co. in the standardization of the oleoresins of capsicum and ginger. This firm has devised a physiological method for this purpose based on the extreme pungency of these preparations, the highest dilutions in which these preparations (on the average) are still perceptible to the taste being taken as standards.

Experiments conducted in the laboratory in preparation for this monograph have shown, not only that there is an opportunity for improving on some of the above mentioned methods, but that there is need for the development of quantitative methods which may be applied to the other individuals of this class as well. With respect to the forepart of this statement, it is thought that a gravimetric method for the estimation of the pungent principles (gingerol) in ginger would be an improvement over the physiological method of the Mulford Co. as personal idiosyncrasy would thus be eliminated. Trials with the method of Garnett and Grier<sup>1</sup>) (for the estimation of gingerol in ginger) adapted to the oleoresin appear to indicate the correctness of this opinion. In the case of the oleoresin of capsicum, however, the physiological method apparently offers the only practical course at the present time, in view of the fact that the active constituent, capsaicin, is present in such minute quantities that an accurate gravimetric determination would be a difficult matter.

In considering the application of new methods, the work done in this laboratory on the oleoresin of pepper may be cited. Since the therapeutical value of this preparation is apparently due to its piperine content, a method for the quantitative determination of this constituent appeared to be desirable. With this object in view, the nitrogen present was determined by the Kjeldahl method and the piperine content computed therefrom. Some very interesting results were obtained.<sup>2</sup>) As to further possibilities along this line the determination of the apiol content of the oleoresin of parsley, or the estimation of the quantity of total acid resins present in the oleoresin of cubeb may be mentioned.

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<sup>1</sup> See under oleoresin of ginger.

<sup>2</sup> See under oleoresin of pepper.

### ADULTERATIONS

The examination of commercial samples of the oleoresins has shown that they are all adulterated at times. With respect to most of these preparations, adulteration is thought to be accidental, *e. g.* the presence of copper in nearly all samples due to the use of copper utensils in the manufacture of the same, or the use of ripe instead of unripe fruits in the preparation of the oleoresin of cubeb. In some cases, however, adulteration has been practiced with willful intention to defraud, as for example, the addition of fatty oils to the oleoresins of aspidium and cubeb. Other instances of this kind will be given consideration under the treatment of the individual oleoresins.

## PART II—INDIVIDUAL OLEORESINS

### OLEORESIN OF ASPIDIUM

#### *Synonyms*

- Aceite de Helecho Macho*, Sp. P. 1905.  
*Aetheres pafran-Kivonat*, Hung. P. 1880.  
*Aetherhaltiges Farrenkrautextract*, Aust. P. 1844.  
*Aetherisches Farrnkrautextract*, Pruss. P. 1830.  
*Aetherisches Farrnkrautwurzel Extract*, Bad. P. 1841.  
*Alvejuuriekstrakti*, Finn. P. 1914.  
*Balsamo de Helecho*, Dorvault, *L'Officine*, Sp. Trans. 1879.  
*Balsamum Filicis*, Pareira, Mat. Med. 1854.  
*Baumé de Fougère*, Dorvault, *L' Officine*, 1898.  
*Braegne-Extract*, Dan. Mil. P. 844.  
*Bregnerod Extract*, Nor. P. 1870.  
*Bregnerodekstrakt*, Nor. P. 1895.  
*Bregnerotekstrakt*, Nor. P. 1913.  
*Estratto di Felce Maschio*, Swiss. P. 1907.  
*Estrato di Felce Maschio Etereo*, Ital. P. 1902.  
*Ethereal Extract of Male Fern*, Journals.  
*Extract of Male Fern*, Jap. P. 1907.  
*Extract van Mannetjes-Varen*, Nethl. P. 1871.  
*Extracto de Feto Macho*, Port. P. 1876.  
*Extracto de Feto Macho Etereo*, Port. P. 1876.  
*Extracto Etereo Helecho*, Sp. P. 1884.  
*Extracto Etereo de Helecho Macho*, Sp. P. 1905.  
*Extracto oleo-resinoso de Helecho*, Dorvault, *L'Officine*, Sp. Trans. 1879.  
*Extractu de Filice Masculae*, Roum. P. 1874.  
*Extractu di Felce Machio*, Swiss. P. 1865.  
*Extractum Aethereum Filicis*, Sp. P. 1884.  
*Extractum Aethericum Filicis*, Fr. P. 1866.  
*Extractum Aethericum Filicis Maris*, Fr. P. 1866.  
*Extractum Aspidii*, Nor. P. 1854.  
*Extractum di Felce Machio Etereo*, Port. P. 1876.  
*Extractum Filicis*, G. P. 1900.  
*Extractum Filicis aethereum*, Pruss. P. 1861.  
*Extractum Filicis liquidum*, B. P. 1914.  
*Extractum Filicis Maris aethereum*, Ital. P. 1902.  
*Extractum Filicis oleoso-resinosum*, Jourdan, Univ. P. 1832.  
*Extractum Radicis Filicis Maris aethereum*, Bad. P. 1841.

- Extractum Stipitum Aspidii*, Nor. P. 1854.  
*Extrait de Fougère*, Belg. P. 1906.  
*Extrait de Fougère Mâle*, F. P. 1908.  
*Extrait Ethéré de Fougère*, Belg. P. 1854.  
*Extrait Ethéré de Fougère Mâle*, Fr. P. 1866.  
*Extrait oléo-résineux de Fougère*, Bern. P. 1852.  
*Extrait oléo-résineux de Fougère Mâle*, Fr. P. 1908.  
*Farnextrakt*, Ger. P. 1900.  
*Farrenkrautextrakt*, Bern. P. 1852.  
*Farnwurzel Extract*, Swiss. P. 1865.  
*Filicis Extractum*, Belg. P. 1906.  
*Filixextrakt*, Journals.  
*Huile de Fougère Mâle*, Belg. P. 1854.  
*Huile de Fougère de Peschier*, Bern. P. 1852.  
*Liquid Extract of Fern Root*, Br. P. 1864.  
*Liquid Extract of Male Fern*, Br. P. 1885.  
*Oil of Filix mas*, Parrish, Treat. on Pharm. 1867.  
*Oil of Male Fern*, Journals.  
*Oleoresin of Fern*, U. S. P. 1870.  
*Oleoresin of Male Fern*, U. S. P. 1910.  
*Oleoresina Aspidii*, U. S. P. 1910.  
*Oleo-resina de Helecho*, Dorvault, L'Officine, Sp. Trans. 1879.  
*Oleoresina Filicis*, U. S. P. 1860.  
*Oleo-Resina Filicis*, Peschter, Ver. P. der Lond., Edinb., and Dub. Med. Coll. 1827.  
*Oléo-résine de Fougère*, Dorvault, L'Officine, 1898.  
*Oleum Filicis*, Hung. P. 1861.  
*Oleum Filicis Maris*, Sp. P. 1905.  
*Oleum Filicis Maris aethereum*, Swiss. P. 1865.  
*Oleum Filicis Peschieri*, Pareira, Mat. Med. 1854.  
*Oleum Filicis pingue resinosum* Geiger's P. 1835  
*Oleum Radicis filicis*, Strump. Allg. P. 18661.  
*Orbunksrot Extrakt*, Swed. P. 1901.  
*Pafran-Kivonat*, Hung. P. 1871.  
*Varenextrakt*, Neth. P. 1905.  
*Wurmfarnextrakt*, Swiss. P. 1893.  
*Wurmfarnoel*, U. S. Disp. 1907.

### History

The oleoresin of aspidium, or *Huile de Fougère Mâle* as it was originally known, was first prepared by Peschier in 1825.<sup>1</sup> The advantages of Peschier's preparation over the forms in which male fern was being administered at the time were quickly noted and it received almost immediate recognition throughout Europe. The rapidity with which it was taken up by the medical profession is evidenced in the fact that it was mentioned in the *Vereinigte Pharmacopœen der Londoner, Edingurgher und Dubliner Medicinæ Collegien*, a German translation of the pharmacopœias of London, Edinburgh and Dublin, which appeared in 1827, and, that two years later (1829), it became official in the Prussian Pharmacopœia. Its introduction into other European pharmacopœias followed, as a general rule, in the chronological order of their appearance or revision, whereas, it was the last of this class of preparations to be admitted to the *United States Pharmacopœia* previous to the ninth revision, having been recognized for the first time in the edition of 1870. At the present time, it is the only preparation of this kind which is official in all of the national pharmacopœias. However, it is only in the United States where it is officially recognized under the title oleoresin, it being classed as an extract in all of the foreign pharmacopœias. For a better appreciation of this fact, see the preceding table of synonyms.

A better idea of the popularity of this preparation and the rate at which it came into prominence will be obtained from the following table in which are chronologically enumerated the names of the pharmacopœias of the countries, states and municipalities where it first received official recognition, also, the dates of appearance of the succeeding editions in which it occurs.

Prussian Pharmacopœia — 1829, 1846, 1862.

Pharmacopœia of Baden — 1841.

Austrian Pharmacopœia — 1844, 1869, 1889, 1906.

Pharmacopœia of Schleswig-Holstein — 1844.

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<sup>1</sup>Gebhardt in 1821, and Morin in 1824, in their analyses of male fern, extracted the rhizomes with ether and obtained what they termed a thick, green, fatty oil. This was, of course, the *Huile de Fougère of Peschier*. Neither of these investigators, however, pointed out its value as a galenical preparation, although, the latter stated that he considered it to be the therapeutically active principle of the rhizomes.

Swedish Pharmacopœia — 1846, 1869, 1879, 1888, 1901, 1908.  
 Pharmacopœia of Berne — 1852.  
 Belgian Pharmacopœia — 1854, 1885, 1906.  
 Norwegian Pharmacopœia — 1854, 1870, 1879, 1895, 1913.  
 Pharmacopœia of Hannover — 1861.  
 Pharmacopœia of Hessa — 1862.  
 British Pharmacopœia — 1864, 1867, 1885, 1898, 1814.  
 Swiss Pharmacopœia — 1865, 1872, 1893, 1907.  
 French Pharmacopœia — 1866, 1884, 1908.  
 Austrian Pharmacopœia — 1869, 1889, 1906.  
 Hungarian Pharmacopœia — 1871, 1888, 1909.  
 Netherlands Pharmacopœia — 1871, 1889, 1909.  
 German Pharmacopœia — 1873, 1882, 1890, 1900, 1910.  
 United States Pharmacopœia — 1870, 1880, 1890, 1900, 1910.  
 Roumanian Pharmacopœia — 1874.  
 Portuguese Pharmacopœia — 1876.  
 Spanish Pharmacopœia — 1884.  
 Italian Pharmacopœia — 1892, 1902, 1909.  
 Danish Pharmacopœia — 1893, 1907.  
 Japanese Pharmacopœia — 1907.  
 Russian Pharmacopœia — 1910.  
 Finnish Pharmacopœia — 1914.

### *Drug Used, Its Collection, Preservation, Etc.*

The rhizomes directed by all of the present day pharmacopœias to be used in the preparation of the oleoresin of aspidium are those of the male fern<sup>1</sup> now referred by botanists to the genus *Dryopteris* as *Dryopteris Filix-mas* (Linné) Schott. As male fern, especially in the older works on pharmacy, has been referred to genera other than *Dryopteris*, the following table of botanical synonyms is given :

<sup>1</sup> The rhizomes of ferns other than those which have been officially recognized are said to yield oleoresins which are active in the expulsion of the tapeworm.

Kuersten states that the rhizomes of *Aspidium athamanticum* Kunze yield a preparation which is as active as that obtained from male fern. Arch. d. Pharm. (1891), 229, p. 258.

Lauren reports the use of an extract in Finland prepared from *Aspidium spinulosum* Sw. which he states is very active as a teniafuge. Finska Laegaresaellck. Handl. (1897), p. 9; Pharm. Centralh., (1897), 39, p. 775.

Rosendahl suggests that the rhizomes of *Dropteris dilatata* replace those of *Dryopteris Filix-mas* in the preparation of the official oleoresin as he has found them to be four times as active as the latter in the expulsion of *Bothryocephalus latus*. Hygienic Lab. Bull. No. 87, p. 250.

*Aspidium Filix-mas* Swartz.  
*Aspidium Mildeanum* Goeppert.  
*Lastrea Filix-mas* Presl.  
*Nephrodium Filix-mas* Michaux  
*Polypodium Filix-mas* Linné.  
*Polystichum Filix-mas* Roth.  
*Tectarea Filix-mas* Cavan.  
*Polypodium-nemorale* Salisbury.  
*Polystichum Durum et induratum* Schur.  
*Polystichum abbreviatum* De Candolle.

In addition to the rhizomes of *Dryopteris Filix-mas* (Linné) Schott, the *United States Pharmacopœia* also permits the use of the rhizomes of *Dryopteris marginalis*, Linné formerly referred to the genus *Aspidium* as *Aspidium marginale* Schwartz. It should be noted in this connection that the official recognition of *Dryopteris marginalis* Linné appears to have been based on the somewhat doubtful statements of but three persons made back in the seventies. These men, Patterson,<sup>1</sup> Cressler,<sup>2</sup> and Kennedy,<sup>3</sup> respectively, reported that they had prepared oleoresins from the rhizomes of this fern. Two of them, Cressler and Kennedy, also stated that their preparations were found to be active in the expulsion of tape worm, while Patterson merely reported that his preparation resembled the German oleoresin of male fern in appearance and taste. There does not appear to be any evidence in the literature to show that an oleoresin authentically prepared from this rhizome was ever given a trial by a reputable physician. Furthermore, there is no evidence to the effect that the rhizome is ever used in preparing the oleoresin at the present time, a statement which has also been made by Rusby.<sup>4</sup>

The definition of *Aspidium* as given in the ninth revision of the *United States Pharmacopœia* is as follows: "The rhizome and stipes of *Dryopteris Filix-mas* (Linné) Schott, or of *Dryopteris marginalis* (Linné) Asa Gray (Fam. *Polypodiaceae*), collected in the autumn, freed from the roots and dead portions of rhizomes and stipes and dried at a temperature not exceeding 70° C. Preserve aspidium in tightly closed containers and protect from light."

<sup>1</sup> Am. Journ. Pharm. (1875), 47, p. 292.

<sup>2</sup> Cressler states that he prepared an oleoresin from what he thought to be male fern, but which later proved to be *Aspidium marginale*. Ibid., (1878), 5, p. 290.

<sup>3</sup> Ibid. (1879), 51, p. 382.

<sup>4</sup> Drugg. Circ. (1910), 54, p. 616.



With further reference to the species of drug specified by the Pharmacopœia, it should be stated that the male fern of commerce, obtained from Europe, is frequently contaminated with the rhizomes of other species of fern, principally those of *Dryopteris spinulosa* Kunze. Pendorff (1903), who examined 20 samples of the commercial drug, reported that 12 of them contained over 50 per cent. of rhizomes of this species.

The pharmacopœial directions concerning the collection of the rhizomes in autumn are in keeping with specifications given in most of the foreign pharmacopœias<sup>1</sup> and are based on the results of extensive investigations carried out in continental Europe and England. Analyses of the drug harvested at different periods of the year have shown autumn to be the season in which the therapeutically active constituents are present in greatest amount. Thus, the firm of Caesar and Loretz, in their *Berichte* for 1898, state that the amount of active constituents present does not begin to approach the maximum until the month of August and that it again begins to diminish in October. They, therefore, conclude that the rhizomes should be harvested only in the months of August, September and October. Similar conclusions were drawn by Ed. Schmidt<sup>2</sup> from a series of observations made in France in 1903. The following table compiled by the latter shows the variation in crude filicin content of the ethereal extracts (oleoresins) prepared from the rhizomes harvested during six consecutive months of the year.

TABLE 8.—*Variation of crude filicin content due to season.*

Time of harvesting	Crude filicin content of oleoresins prepared from rhizomes gathered in the —			
	Forest near Paris	Jura Mts.	Vosges Mts.	Vosges Mts. Peeled Rhiz.
	Per cent	Per cent	Per cent	Per cent
May.....	9.70	12.78	13.76	—
June.....	10.80	13.86	15.65	12.75
July.....	10.86	14.60	17.70	14.85
August.....	11.64	17.80	19.70	15.60
September.....	13.78	19.60	20.76	17.76
October.....	11.80	18.68	19.80	16.70

<sup>1</sup> The Spanish Pharmacopœia (1905) directs that the rhizomes be collected at the end of spring or in the autumn.

<sup>2</sup> *Thèse pour l'obtention du Diplôme de Docteur de l'Université de Paris* (1903), p. 116.

The table not only shows a variation in the crude filicin content due to season, but also points out the fact that there is a very considerable variation due to the locality<sup>1</sup> in which the rhizomes are grown. This factor, while evidently overlooked by the United States Pharmacopoeial Revision Committee, appears to be of considerable importance in influencing the quality of the oleoresin. Further proof of this is to be found in the reports of Van Aubel,<sup>2</sup> Madsen,<sup>3</sup> Matzdorff,<sup>3</sup> and Caesar and Loretz.<sup>4</sup>

Further inspection of the pharmacopoeial definition shows that the official drug is intended to be represented by the whole rhizome and stipe deprived only of the roots and dead portions, which is also in conformity with the description generally found in foreign pharmacopoeias. This is a wise provision in that the rhizomes not only contain less of the active constituents when peeled<sup>5</sup> but deteriorate much more rapidly. On the other hand, compliance with this specification would appear to be a difficult problem for the pharmacist as practically all of the drug on the American market is peeled. The latter statement is based on the examination of a number of samples in the laboratory<sup>6</sup> and on the reports of pharmaceutical manufacturers<sup>7</sup> and others<sup>8</sup>.

In the drying of the rhizomes, the *United States Pharmacopoeia* specifies that the temperature shall not exceed 70°C. This temperature is thought to be too high, as filmaron, the most active constituent therapeutically, melts at 60°C and is very prone to undergo decomposition.<sup>9</sup> The directions as given

<sup>1</sup> A variation due principally to soil and climate.

<sup>2</sup> Van Aubel (1896) states that the rhizomes growing in Wolmar on the shores of the Aa and those growing in the Jura and Vosges mountains yield an oleoresin which is more active therapeutically than that prepared from the rhizomes growing in Italy.

<sup>3</sup> Madsen (1897) and Matzdorff (1901) report the oleoresin prepared from Russian rhizomes to be the most active.

<sup>4</sup> Caesar and Loretz attribute the uniform activity of the oleoresin prepared by them to the fact that they obtain their supply of rhizomes from the same locality each year.

<sup>5</sup> See preceding table by Schmidt.

<sup>6</sup> Of the sixteen samples of male fern rhizomes purchased from various sources in the United States and examined in the laboratory all but three were in the peeled condition.

<sup>7</sup> Letters received from a number of pharmaceutical manufacturers in this country indicate that the drug as usually received from Europe is peeled.

<sup>8</sup> Plaut (1914) states that though the *U. S. Pharmacopoeia* requires the use of unpeeled aspidium, none such is to be found on the market.

<sup>9</sup> Kraft (1902).

in the Belgian Pharmacopœia (1906), "dry at a temperature below 40°C," or the Norwegian Pharmacopœia (1914), "dry at a temperature not exceeding 60°C," appear to be more rational.

In connection with the pharmacopœial provision concerning the preservation of the drug, attention is called to the fact that the late edition of the German Pharmacopœia (1910) requires that the dried rhizomes be kept over freshly calcined lime. Such a procedure was shown by Hager, as early as 1871, to render the oleoresin prepared therefrom less liable to form a deposit.

The fact that the *United States Pharmacopœia* does not specify a time limit for the consumption of the drug is unfortunate in view of the rapidity with which it is known to deteriorate.<sup>1</sup> So important is this factor, that the French Pharmacopœia (1908) directs that only the recently collected and freshly dried rhizomes be employed and the other European pharmacopœias commonly specify that they be renewed annually. That there is need of similar restrictions in this country will become evident from the following table showing the results obtained in the examination of fourteen samples of commercial rhizomes. Six of these samples were purchased from importers and drug millers in the United States during the winter and spring of 1909 and 1910, respectively. The other specimens were received in January of 1913 and represent samples obtained from abroad as well as in this country. In each case, the rhizomes were sorted, those showing a green fracture having been separated from those showing an internal brown color.

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<sup>1</sup> Peschier as early as 1825 noted that the therapeutic activity of the rhizomes diminished on ageing and recommended that they should be consumed within a period of less than two years after harvesting.

Caesar and Loretz state that they prepare the year's supply of oleoresin immediately after harvesting and drying the rhizomes to insure the maximum activity of the preparation.

TABLE 9.—Percentage of green rhizomes in samples of male fern purchased from drug millers and jobbers.

Sample No.	Date of purchase	Source	Content of green rhizomes
			Per cent.
1.....	December, 1909.....	United States.....	6.5
2.....	" ".....	" ".....	18.0
3.....	" ".....	" ".....	0.0 <sup>1</sup>
4.....	April, 1910.....	" ".....	8.0
5.....	" ".....	" ".....	0.0
6.....	" ".....	" ".....	53.7
7.....	January, 1913.....	" ".....	0.0
8.....	" ".....	" ".....	9.2
9.....	" ".....	England.....	0.0
10.....	" ".....	" ".....	0.0
11.....	" ".....	Germany.....	4.2
12.....	" ".....	" ".....	8.5
13.....	" ".....	France.....	0.0
14.....	" ".....	" ".....	0.0

<sup>1</sup> Composed entirely of *Osmunda* rhizomes.

It will be noticed that even the rhizomes purchased in Germany were not in good condition. As these rhizomes were obtained in January, they should have shown an internal green coloration had they consisted of the fresh stock harvested in the preceding autumn. From this, it appears that the German supply for exportation, at least, is not renewed yearly as it should be, but is allowed to accumulate and deteriorate.

#### *U. S. P. Text and Comments Thereon.*

Oleoresin of aspidium was admitted to the *United States Pharmacopœia* in 1870 and has been official in all subsequent editions.

1870

#### Oleoresina Filicis

#### Oleoresin of Fern

Take of Male Fern,<sup>1</sup> in fine powder,<sup>2</sup> pour ether upon it, until twenty-four twelve troyounces; Ether<sup>4</sup> a sufficient quantity.

Put the male fern into a cylindrical glass percolator, provided with a stop-cock, and arranged with cover and receptacle suitable for volatile liquids,<sup>5</sup> press it firmly, and gradually

pour ether upon it, until twenty-four fluidounces of liquid have slowly passed.<sup>6</sup> Recover<sup>7</sup> the greater part of the ether by distillation on a water-bath, and expose the residue, in a capsule, until the remaining ether has evaporated.<sup>8</sup> Lastly, keep the oleoresin in a well-stopped bottle.<sup>9</sup>

1880

## Oleoresina Aspidii

## Oleoresin of Aspidium

[Oleoresina Filicis, Pharm., 1870]

Aspidium,<sup>1</sup> in No. 60 powder,<sup>2</sup> *one* ether by distillation on a water-bath, *hundred parts* .....100. and expose the residue, in a capsule, Stronger Ether,<sup>4</sup> *a sufficient quantity.* until the remaining ether has evaporated.<sup>5</sup>

Put the aspidium into a cylindrical glass percolator, provided with a cover and receptacle suitable for volatile liquids,<sup>6</sup> press it firmly, and gradually pour stronger ether upon it, until one hundred and fifty (150) parts of liquid have slowly passed.<sup>8</sup> Recover<sup>7</sup> the greater part of the

Keep the oleoresin in a well stopped bottle.<sup>9</sup>

Note. Oleoresin of aspidium usually deposits, on standing, a granular crystalline substance.<sup>10</sup> This should be thoroughly mixed with the liquid portion, before use.<sup>11</sup>

1890

## Oleoresina Aspidii

## Oleoresin of Aspidium

Aspidium,<sup>1</sup> recently<sup>2</sup> reduced to No. 60 powder,<sup>3</sup> *five hundred grams* ..... 500 Gm. of the ether from the percolate by distillation on a water-bath, and, having transferred the residue to a capsule, allow the remaining ether to evaporate spontaneously.<sup>5</sup>

Put the aspidium into a cylindrical glass percolator, provided with a stop-cock, and arranged with cover and receptacle suitable for volatile liquids.<sup>6</sup> Press the drug firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted.<sup>8</sup> Recover the greater part

Keep the oleoresin in a well-stoppered bottle.<sup>9</sup>

NOTE. Oleoresin of Aspidium usually deposits, on standing, a granular-crystalline substance.<sup>10</sup> This should be thoroughly mixed with the liquid portion before use.<sup>11</sup>

1900

## Oleoresina Aspidii

## Oleoresin of Aspidium

Aspidium,<sup>1</sup> recently<sup>2</sup> reduced to No. 40 powder,<sup>3</sup> *five hundred grammes* transferred the residue to a dish, al-

..... 500 Gm. low the remaining acetone to evaporate spontaneously in a warm place.<sup>4</sup>

Acetone,<sup>4</sup> *a sufficient quantity*.  
Introduce the Aspidium into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle suitable for volatile liquids.<sup>5</sup> Pack the powder firmly and percolate slowly with acetone, added in successive portions, until the Aspidium is exhausted.<sup>6</sup> Recover<sup>7</sup> the greater part of the acetone from the percolate by distilla-

tion on a water-bath, and, having transferred the residue to a dish, allow the remaining acetone to evaporate spontaneously in a warm place.<sup>8</sup> Keep the oleoresin in a well-stoppered bottle.<sup>9</sup>

NOTE. Oleoresin of aspidium usually deposits, on standing, a granular crystalline substance.<sup>10</sup> This should be thoroughly mixed with the liquid portion before use.<sup>11</sup>

Average dose ..... 2 Gm. (30 grains).

1910

## Oleoresina Aspidii

## Oleoresin of Aspidium

## Oleores. Aspid.—Oleoresin of Male Fern

Aspidium,<sup>1</sup> recently<sup>2</sup> reduced to No. 40 powder,<sup>3</sup> *five hundred grammes* ..... 500 Gm. having transferred the residue to a dish, allow the remaining ether to evaporate spontaneously in a warm place.<sup>4</sup> Keep the oleoresin in a well-stoppered bottle.<sup>5</sup>

Ether,<sup>4</sup> *a sufficient quantity*.

Place the aspidium in a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle suitable for volatile liquids.<sup>5</sup> Pack the powder firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted.<sup>6</sup> Recover<sup>7</sup> the greater part of the ether from the percolate by distilling on a water bath, and,

NOTE.—Oleoresin of Aspidium, on standing, usually deposits a granular crystalline substance.<sup>8</sup> This should be thoroughly mixed with the liquid portion before use.<sup>11</sup>

Average Dose—Caution! Single dose, once a day, Metric, 2 Gm.—Apothecaries, 30 grains.

1.) The Pharmacopoeia of 1870 recognized but one species of fern (*Aspidium Filix-mas*) as the source of the official drug, hence, the directions: "Take of Male Fern, etc." In the subsequent editions, *Aspidium marginale* was also recognized as a source of supply. In these editions, the drug is, therefore, referred to by the generic name, *Aspidium*. The species from which the official drug is obtained are now referred by botanists to the genus *Dryopteris*. See page 969 under "Drug used, its collection, preservation, etc."

2.) Owing to the fact that the drug deteriorates rapidly when in the powdered condition, the last three editions of the Pharmacopœia have specified that the rhizomes be preserved whole and that they may be reduced to a powder shortly before using. For factors causing the deterioration of the drug, see under "Drug used, its collection, preservation, etc."

3.) In the last two editions of the Pharmacopoeia, it is directed that the drug be employed in the form of a moderately coarse powder (No. 40). In the previous editions, a fine powder (No. 60) was specified. The coarser powder possesses distinct advantage in that it is better adapted to percolation and can be produced with a greater degree of uniformity.

4.) It will be observed that the pharmacopœias of 1870, 1880 and 1890 directed that the drug be extracted with ether; that acetone was the menstruum specified in the Pharmacopœia of 1900; and that ether is again directed to be used for this purpose by the present Pharmacopœia.

These changes appear to have been made for economic reasons as is evidenced in the following statement by Beringer (1916): "In the Eighth Revision, acetone was directed in place of ether, because at that time the former was cheaper. As it is now permissible to use denatured alcohol in the manufacture of ether, that solvent is made so cheaply that it is again advantageous to use it in place of acetone." If the comparative cost of the two solvents was the factor which induced the Revision Committee to make the last change, it is indeed fortunate that ether was the cheaper inasmuch as it has proven to be the more desirable from a scientific standpoint as well.

Acetone, although the official menstruum for the preparation of this oleoresin for more than a decade, does not appear to have been employed for this purpose to any considerable ex-

tent by the manufacturer. This statement is based upon the examination of a number of commercial samples purchased at various times during the past ten years. While the reason for the above condition does not become apparent from the literature, it is thought that it is to be attributed to the fact that acetone yields a product of inferior quality, rather than to the relatively low cost of ether. In support of this supposition, attention is called to the statement of Dunn (1909), who reports that it is necessary to purify the oleoresin made with acetone by dissolving the same in ether, also, to the observations made in the laboratory.

Experiments conducted in the laboratory have shown that the oleoresin, when prepared with acetone, is brown in color and always contains considerable deposited matter. While the greater bulk of the deposited material has the appearance of extractive matter and is very likely of no consequence from a therapeutical standpoint, portions of it answer to the descriptions of filixnigrin and filix acid, decomposition products of the therapeutically active constituents. The latter observation is in keeping with that of Kraft (1902), who found that filmaron, the most important of the therapeutically active constituents, decomposes in acetone solution yielding the above mentioned decomposition products. It was also noted that the amount of deposited material increases much more rapidly in the preparations made with acetone than in those in which ether was used as the menstruum for extracting the drug.

As previously stated, ether has proven to be the more satisfactory solvent for scientific as well as economic reasons. In fact it has been found to be superior to any of the solvents which have been experimented with in this connection, namely: benzin, benzene, chloroform and carbon disulphide. See Part I, page 921, under "Solvents." At the present time, it is the solvent universally employed in the manufacture of the oleoresin, which is in itself a good reason for its adoption by the Pharmacopoeia. Furthermore, the product obtained with ether is perfectly homogenous and forms a deposit only after long standing, the constituents of therapeutic value evidently undergoing no decomposition in ethereal solution. However, the quality of the preparation, even when ether is employed in extracting the drug, is influenced to a certain extent by the purity of the solvent.



Alcohol and water appear to be the impurities which tend to exert a deleterious influence upon the finished product. Thus, Dacomo and Scoecianti (1896) observed that ether containing a considerable amount of alcohol did not completely extract the therapeutically active constituents from the drug and that the oleoresin obtained was more prone to form a deposit than when ether of a greater degree of purity was used. See also page 984 under "Yield of oleoresin." Similar effects were observed by the firm of Caesar and Loretz (1899.) The presence of water is so great a factor in promoting decomposition (hydrolysis?) that the German Pharmacopœia (1910) directs that the rhizomes be preserved over freshly burned lime, a procedure which was recommended by Hager as early as 1871. Further evidence of the undesirability of the presence of water is to be found in the Norwegian (1913) and Finnish (1914) pharmacopœias, which direct that the ethereal tincture be dried with anhydrous sodium sulphate or fused calcium chloride previous to the removal of the solvent by distillation.

5.) For a description of the various forms of percolators designed for extraction with volatile solvents, see Part I under "Apparatus used."

6.) All editions of the Pharmacopœia, including the present, direct that the drug be extracted by the process of simple percolation even though the advantages of a continuous extraction apparatus in the handling of a volatile solvent like ether have been repeatedly pointed out. See Part I under "Solvents" and under "Apparatus used."

Of special interest in this connection is the work of Matzdorff (1901), the results of which show that the therapeutically active constituents are not completely extracted by simple percolation as ordinarily carried out, but that complete extraction is effected in a comparatively short time with the use of a Soxhlet's apparatus.

7.) In connection with the recovery of the solvent by distillation, attention is again directed to the deleterious effect of the presence of moisture and to the manner in which the same is directed to be removed by the Norwegian and Finnish pharmacopœias. See above.

Attention is also invited to the pharmacopœial directions regarding distillation, namely that it be conducted on a water

bath. Inasmuch as Kraft (1902) states that filmaron melts at 60°C and undergoes decomposition at higher temperatures, it is thought that the pharmacopoeial directions should contain a warning against exceeding this temperature during distillation.

8.) The removal of a part of the solvent by spontaneous evaporation as directed by the Pharmacopœia tends to operate against obtaining a uniform product as the time required to accomplish the same varies with the temperature. If evaporation is allowed to proceed at a low temperature (winter temperature), the preparation will be exposed to the action of the air for a very considerable length of time and partial oxidation of some of the constituents will very likely result.

The complete removal of the solvent can be accomplished much more rapidly by heating the preparation on a water bath, and without injury, if the temperature is kept below 60°C. By such a procedure, the above conditions are eliminated and a more uniform product will be obtained.

9.) The oleoresin should be kept in well-stoppered bottles as it becomes rancid on prolonged exposure to the air due to the hydrolysis and partial oxidation of the glycerides composing the fatty oil.

10.) For a discussion of the nature of the deposit which forms in the oleoresin on standing, see pages 992 and 1004 under "Constituents of therapeutic importance," and under "Other properties."

11.) As to the propriety of the pharmacopœial directions concerning the mixing of the deposit with the liquid portion before dispensing, there is some doubt. The question, however, is one which should be decided by the pharmacologist rather than the pharmacist and will, therefore, not be considered here.

The use of an alkali, ammonia as suggested by Beringer (1892), for the purpose of facilitating the admixture of the precipitate with the liquid portion should be condemned as a dangerous practice. The danger lies in the fact that the slightly soluble toxic constituents are converted into soluble compounds by union with the alkali and are thereby rendered readily absorbable.

Of further interest in this connection is the procedure recommended by Seifert (1881) and Kraemer (1884) for avoiding

the formation of a deposit, namely: that the ethereal tincture be kept on hand and that the oleoresin be prepared therefrom just previous to dispensing.

### *Yield*

The yield of oleoresin, when ether is the solvent employed in extracting the drug, is commonly stated to be 10 to 15 per cent. in the various dispensatories and American text-books on pharmacy. As a matter of fact, the amount of oleoresin actually obtained is about 7 to 10 per cent. (See the tables which follow.) When petroleum ether or benzene is used, the yield is slightly lower, as a rule, whereas, it is much higher (about 18 per cent.) when acetone is employed. These statements refer to the yield as found for the air dried drug. When the latter is dried at a temperature of 100 to 110°C, the percentage of oleoresin obtained will naturally be somewhat higher as is shown in the table immediately following.

TABLE 10.—Yield of oleoresin as reported in the literature.

Date	Observer	Yield of oleoresin to				Remarks
		Alcohol	Acetone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per ct.	
1826	von Esenbeck .....	.....	.....	5.63	.....	Rhizomes harvested in August.
1827	Van Dyk .....	37.5	.....	7.30	.....	Rhizomes harvested in September.
	Zeller .....	32.0	.....	.....	.....	
1828	Meylink .....	.....	.....	6.04	.....	Rhizomes harvested in February.
	Winkler .....	15.6	.....	.....	.....	
1829	Haendess .....	.....	.....	8.85	.....	Peeled rhizomes dried at 100° C.
1844	Hornung .....	.....	.....	8.33	.....	
1851	Bock .....	.....	.....	12.87	.....	
1852	von der Marck .....	.....	.....	7.80	.....	Portion of rhizomes having borne fronds the previous year.
		.....	.....	8.20	.....	Portion of rhizome bearing fronds.
		.....	.....	8.50	.....	Portion of rhizome to develop fronds the next year.
1876	Kruse .....	.....	.....	10.30	{ Petrol. Ether 9.3	Rhizomes harvested in April. Dried at 110° C.
		.....	.....	12.40	{ 3.4	
		.....	.....	11.50	{ 9.1	
1887	Kremel .....	29.0	.....	14.00	{ Benzin 5.9	Rhizomes harvested in October. Dried at 110° C.
1888	Trimble .....	.....	.....	6.51	.....	Rhizomes harvested in July, 1889.
1891	Nagelwoort (1) .....	.....	.....	5.60	.....	
		.....	.....	6.20	.....	
		.....	.....	5.70	.....	
		.....	.....	6.00	.....	
		.....	.....	8.50	.....	
		.....	.....	8.00	.....	
		.....	.....	11.00	.....	
		.....	.....	13.00	.....	
		.....	.....	6.00	.....	
		.....	.....	6.50	.....	
		.....	.....	5.70	.....	
1892	Berlinger .....	.....	18.0	.....	{ Benzin 16.18	Whole Rhizomes.
	Sherrard .....	.....	.....	9.27	.....	Peeled "
		.....	.....	9.87	.....	
		.....	.....	7.26	.....	
		.....	.....	8.90	.....	
1898	Bellingrodt .....	.....	.....	5.90	.....	Rhizomes from "Rheinische Tiefebene (Calcar)."
		.....	.....	6.12	.....	Rhizomes from "Rheinische Tiefebene (Dinslaken)."
		.....	.....	8.92	.....	Rhizomes from "Voreifel (Aachen)."
		.....	.....	9.96	.....	Rhizomes from "Hocheifel (Gerolstein)."
		.....	.....	9.50	.....	Rhizomes from "Taunus (Braubach)."
		.....	.....	9.88	.....	Rhizomes from "Westerwald auf Thonschiefer (Daaden)."

<sup>1</sup> Ed. Schmidt, Thèse pour l'Obtention du Diplôme du Docteur l'Université de Paris, 1903, p. 78.

TABLE 10.—Continued.

Date	Observer	Yield of oleoresin to				Remarks
		Alcohol	Acetone	Ether	Other solvents	
1887	Bellingrodt— Con.	Perct.	Perct.	Perct.	Per ct.	Rhizomes from "Westerwald auf Basalt boden (Daaden.)"
		.....	.....	9.95	.....	Rhizomes from "Hansruck (Simmern)"
1899	Hausmann	.....	.....	8.90	.....	Rhizomes from "St. Gallen, Switzerland."
		.....	.....	8.50	.....	Rhizomes from "Bludenz (Vorarlberg)."
		.....	.....	10.00	.....	Rhizomes from "Appenzell, Switzerland."
		.....	.....	8.00	.....	Rhizomes from "Bierberwier, Tyrol."
1902	Buttin	.....	.....	9.80	.....	Rhizomes harvested in spring.
1903	Schmidt, E. (1)	.....	.....	8.00	.....	Whole rhizomes from near Paris harvested in September.
		.....	.....	6.60	.....	Whole rhizomes from the Vosges Mts. harvested in September.
		.....	.....	9.60	.....	Whole rhizomes from the Jura Mts. harvested in September.
		.....	.....	9.10	.....	Peeled rhizomes from the Vosges Mts. harvested in September.
		.....	.....	6.40	.....	Whole rhizomes from near Paris harvested in October.
		.....	.....	6.90	.....	Whole rhizomes from the Vosges Mts. harvested in October.
		.....	.....	9.80	.....	Whole rhizomes from the Jura Mts. harvested in October.
		.....	.....	9.30	.....	Whole rhizomes from the Vosges Mts. harvested in October.
		.....	.....	7.00	.....	Peeled rhizomes from the Vosges Mts. harvested in October.
1905	Dietrich	.....	.....	9.94 to 10.60	.....	From air dried rhizomes.
		.....	.....	Up to 11.20	.....	From rhizomes dried at 100° C.
1906	Röder	.....	.....	9.22 to 10.1	.....	Yield obtained when the product was heated at 95° C for 2 hours, cooled in a desiccator & weighed.
1906	Wollenweber	.....	.....	10.30	Benzene 9.81	Air dried rhizomes extracted in a Soxhlet's apparatus.
		.....	.....	10.00	10.10	Exiccated rhizomes extracted in a Soxhlet's apparatus.
		.....	.....	.....	Petrol. Ether 9.8	Air dried rhizomes extracted in a Soxhlet's apparatus.
		.....	.....	.....	9.5	Exiccated rhizomes extracted in a Soxhlet's apparatus.

TABLE 10.—Continued.

Date	Observer	Yield of oleoresin to				Remarks
		Alcohol	Acetone	Ether	Other solvents	
		Perct.	Perct.	Per ct.	Per ct.	
1908	Vanderkleed <sup>(1)</sup>	.....	.....	.....	Solvent? 6.68 10.003 17.90 10.33	Reported as yield of oleoresin.
1909	Vanderkleed..	.....	.....	.....		
1911	Rosendahl.....	.....	.....	10.00		
		.....	.....	12.50		Rhizomes harvested in May.
		.....	.....	11.50	.....	Rhizomes harvested in August.
1913	Harrison & Self	.....	.....	9.50	.....	Rhizomes harvested in October.
		.....	.....	11.60	.....	Rhizomes from "Harz."
		.....	.....	8.80	.....	" " " "
		.....	.....	7.90	.....	" " " "
		.....	.....	8.30	.....	" " " "
		.....	.....	7.70	.....	" " "Bayern"
		.....	.....	9.70	.....	" " " "
		.....	.....	8.60	.....	" " " "
		.....	.....	7.50	.....	" " { "Schwarz- wald, Wuert- temberg."
		.....	.....	7.00	.....	" " { "Mosel, Rhein- Preussen."
914	Riedel .....	.....	.....	10.90	.....	"
		.....	.....	9.40 to	.....	
		.....	.....	9.70	.....	
	Vanderkleed..	.....	.....	.....	Solvent? 6.85 to 10.12	Average yield of oleoresin is reported as 8.23 per cent.
		.....	.....	.....		

<sup>1</sup> The high yield (1.79 per cent.) obtained in this instance is suggestive of the use of acetone as the menstruum for exhausting the drug. It may, however, have been due to the extensive adulteration of the latter with the rhizomes of *Dryopteris spinulosa*. Rosendahl (1911) obtained 17.0 per cent. of oleoresin from the rhizomes of this species by extraction with ether.

TABLE 11.—Yield of oleoresin obtained in the laboratory.

Date	Observer	Yield of oleoresin to				Remarks
		Alcohol	Acetone	Ether	Benzin	
		Per ct.	Per ct.	Per ct.	Per ct.	
1909	DuMez & Baker.....	.....	18.27	9.3	.....	Represents the yield using a Soxhlet's extraction apparatus.
"	DuMez & Beedle.....	.....	.....	9.7	.....	Represents the yield using a Soxhlet's extraction apparatus.
1910	DuMez & Netzel.....	43.33 <sup>(1)</sup>	16.10	8.70	7.5	Represents the yield using a Soxhlet's extraction apparatus.

<sup>(1)</sup> The alcoholic extract was obtained by simple percolation.

An examination of the first of the foregoing tables reveals the fact that the yield is influenced to a very considerable extent by the condition of the drug from which the oleoresin is prepared. Thus, for instance, the amount obtained is less when the powdered whole rhizomes are used than when peeled rhizomes are employed. This is to be expected in view of the fact that the outer layers contain little that is soluble in the solvent (ether) usually made use of. It will also be noticed that natural causes, such as, locality in which the rhizomes are grown, and time of harvesting are important factors in this connection. These influences will be brought out more clearly on an inspection of the following table which shows the results of this nature obtained by Ed. Schmidt.

TABLE 12.—*Effect of locality in which the rhizomes are grown and the time of harvesting on the yield of oleoresin.*

Time of harvesting	Peeled rhizomes from—			Whole rhizomes from—
	Forest near Paris	Vosges Mts.	Jura Mts.	Vosges Mts.
	Per cent.	Per cent.	Per cent.	Per cent.
May .....	4.00	7.00	6.40	.....
June .....	4.80	7.00	7.00	4.90
July .....	5.60	8.70	8.00	5.70
August .....	6.20	9.00	8.40	6.00
September .....	6.00	9.60	9.10	6.40
October .....	6.90	9.80	9.80	7.00

In addition to the comments already made with regard to the influence of the solvent on the yield, the observations of Dacomo and Secocianti (1896) are of importance in this connection. These investigators found that the amount of oleoresin obtained, when ether was employed for extracting the drug, depended to some extent on the purity of the former. Thus, ether, specific gravity 0.720 gave 10 per cent. of oleoresin, whereas, ether, specific gravity 0.756 yielded 17 per cent. It was further pointed out, however, that the greater yield was not desirable as in this case the preparation did not contain all of the therapeutically active constituents and in addition was more prone to form a deposit on standing.

*Chemistry of the Drug and Oleoresin.**Tabulation of Constituents.*

A survey of the voluminous literature<sup>1</sup> pertaining to the chemistry of the male fern rhizome shows the constituents of pharmaceutical interest to be as follows: volatile oil, fatty oil, filix acid, albaspidin, flavaspidic acid, aspidinol, flavaspidinin (phloraspin), filmaron, filixnigrin, chlorophyll, filix tannic acid, wax, sugar, starch and inorganic constituents. Of these substances, the following have been identified in the oleoresin obtained by extracting the drug with ether:

Volatile oil <sup>2</sup> .....	0.40 to 0.45	per cent
Fatty oil <sup>3</sup> .....	70.00 to 75.00	" "
Filix acid <sup>4</sup> .....	5.75 to 12.48	" "
Albaspidin <sup>5</sup> .....	Av. 0.05	" "
Flavaspidic acid <sup>5</sup> .....	" 2.50	" "
Aspidinol <sup>5</sup> .....	" 0.10	" "
Flavaspidinin <sup>5</sup> .....	" 0.10	" "
Filmaron <sup>5</sup> .....	" 5.00	" "

<sup>1</sup> The following have reported more or less complete analyses of the male fern rhizome or of the ethereal extract: Gebhardt, cited by Geiger, *Mag. f. Pharm.* (1824), 7, p. 38; Morin, *Journ. de Pharm. et de Chim.* (1824), 10, p. 223; Buchner, *Rep. f. d. Pharm.* (1827), 27, p. 337; Batso, *Trommsdorff's n. Journ. d. Pharm.* (1827), 14, p. 294; Peschier, *Ibid.* (1828), 17, p. 9; Luck, *Jahrb. f. prakt. Pharm.* (1851), 14, p. 129; Bock, *Arch. d. Pharm.* (1851), 115, p. 257; Kruse, *Ibid.* (1876), 209, p. 24; Dacomo, *Annali di Chim. et Farmak.* (1887), 87, p. 69; Boehm, *Arch. f. Exp. Path. u. Pharmak.* (1896), 38, p. 35; Kraft, *Schweiz. Wochenschr. f. Chem. u. Pharm.* (1902), 40, p. 322.

<sup>2</sup> The percentage of volatile oil as given above has been computed on the basis of an average yield of 10 per cent. of oleoresin.

<sup>3</sup> The quantity of fatty oil present in the oleoresin has been shown to vary with the strength of the ether employed in extracting the drug and with the degree to which the latter has been exhausted. These factors, however, are not sufficient to explain the large variation in oil content as found by various investigators. The variation is more probably due to the different methods employed in its estimation. Thus, Bock reports the presence of 42 per cent of fatty oil, *Arch. d. Pharm.* (1851), 115, p. 266; Kremel estimates it at 40 to 45 per cent, *Pharm. Post d. Pharm.* (1887), 20, p. 525; Wollenweber at 70 to 75 per cent, *Arch. d. Pharm.* (1906), 244, p. 467.

<sup>4</sup> There is a very considerable difference in the filix acid content of the oleoresin as reported in the literature. This is due, principally, to the natural variation in the filix acid content of the drug and to the different methods employed in its estimation. The limits as given above are those obtained by the method of Fromme and represent the percentage occurring in the oleoresin prepared from the better rhizomes. Under these conditions, Madsen found 5.8 to 12.1 per cent, *Arch. f. Pharm. og. Chem.* (1897), 54, p. 269; Gehe & Co., 5.78 to 11.32 per cent, *Handels-Ber.* (1897), p. 60; Bellingrodt, 5.75 to 10.75 per cent, *Apoth. Ztg.* (1898), 13, p. 869; Caesar and Loretz, 8.65 to 12.48 per cent, *Geschaefts-Ber.* (1901), p. 68.



Filixnigrin <sup>8</sup> .....	" " 6.00 " "
Chlorophyll <sup>9</sup> .....	— " "
Wax <sup>7</sup> .....	— " "
Ash .....	" 3.50 to 5.00 " "

### Occurrence and Description of Individual Constituents.

**Volatile oil.**<sup>8</sup> The volatile oil as described by Ehrenberg is a clear yellow liquid having a specific gravity of 0.85 to 0.86 at 15°C, and is stated by him to be composed principally of fatty acid esters of hexyl and octyl alcohol, the acids ranging from propionic to caproic.

The quantity of essential oil present in the rhizomes is stated to vary with the seasons of the year, 0.04 to 0.045 per cent. being contained therein at the time of the year when the drug is usually collected.<sup>9</sup>

**Fatty oil.**<sup>10</sup> The fatty oil as obtained from the male fern rhizomes by extraction with ether and subsequent purification is stated by Katz<sup>11</sup> to be composed of the glyceryl esters of oleic, palmitic, cerotic and butyric acids.<sup>12</sup>

**Filix acid**<sup>13</sup> (*Filicin*)<sup>14</sup> Filix acid ( $C_{35}H_{55}O_{12}$ ) crystallizes

<sup>8</sup> Kraft, Schweiz. Wochenschr. f. Chem. u. Pharm. (1902), 40, p. 323.

<sup>9</sup> Bock, Arch. d. Pharm. (1851), 115, p. 266.

<sup>7</sup> Kraft, l. c.

<sup>8</sup> The volatile oil as described above is that obtained from the rhizomes by steam distillation and in all probabilities differs somewhat from the same as it exists in the galenical oleoresin.

<sup>9</sup> Ehrenberg reports the presence of volatile oil as follows: rhizomes gathered in April, 0.008 per cent; in June .025 per cent; in September, October and November, 0.04 and 0.045 per cent. Arch. d. Pharm. (1893), 231, p. 345.

<sup>10</sup> The fatty oil of male fern was probably first isolated by Luck. In 1851, he reported that the oily portion (*filixoline*) of the ethereal extract was a glyceride yielding *filomysilsaeure* and *filixolinsaeure* upon saponification. Jahrb. f. prakt. Pharm. (1851), 22, p. 130.

From Luck's description it is considered that these acids were in all probability butyric and oleic, respectively.

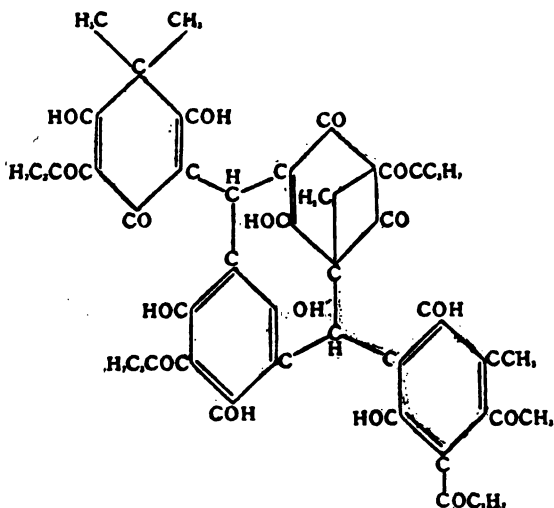
<sup>11</sup> Arch. d. Pharm. (1898), 236, p. 655.

<sup>12</sup> Butyric and oleic acids have also been identified by Farup in the fatty oil obtained from *Aspidium Spinulosum*. In addition a phytosterol, linolinic, and probably isolinolinic acid are stated to have been detected. Arch. d. Pharm. (1904), 242, p. 17.

<sup>13</sup> The term *filixaeure* was first used by Luck to designate this constituent. Filix acid is the translation given above rather than the usual English form, *filic acid*, to avoid confusion with the *filixaeure* of Boehm, a reduction product of the former, Ann. d. Chem. (1899), 307, p. 249, or the *Acidum filiceum* of Batso, a supposedly volatile acid which the latter isolated from the ethereal extract. Tromsdorff's n. Journ. d. Pharm. (1827), 14, p. 249.

<sup>14</sup> *Filicin* is the term introduced by Poulsson to designate the crystalline form of filix acid as he was of the opinion that it also existed in the amor-

in small yellow plates melting at 184 to 185° C. It is difficultly soluble in water, alcohol, and ether, quite readily soluble in ethyl acetate. According to Boehm,<sup>15</sup> its constitution<sup>16</sup> is probably represented by the following structural formula:



Filix acid has been found to be present in the male fern rhizome<sup>17</sup> in quantities varying from 0.268 to 2.159 per cent, the variation in content depending principally upon the location in which the rhizomes are grown and on the time of harvesting.<sup>18</sup>

phous state. Arch. f. Exp. Path. u. Pharm. (1895), p. 357. The term is now usually employed to designate the mixture of acid substances obtained in the quantitative evaluation of the oleoresin. It should not be confused with the *Filicina* of Batso, supposedly an alkaloid isolated from the ethereal extract. l. c.

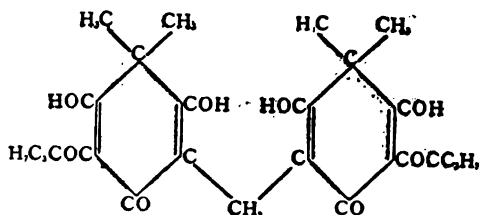
<sup>15</sup> Ann. d. Chem. (1901), 318, p. 256.

<sup>16</sup> The following investigators have contributed work on the constitution of filix acid: Luck, Ann. d. Chem. (1845), 54, p. 119; Jahrb. f. prakt. Pharm. (1851), 22, p. 129; Grabowski, Ann. d. Chem. (1867), 143, p. 279; Dacomo, Ber. d. deutsch. Chem. Gesell. (1888), 21, p. 2962; Gaz. Chim. Ital. (1895), 24, 1, p. 511; Ibid. (1896), 26, 2, p. 441; Paterno, Ber. d. deutsch. Chem. Gesell. (1889), 22, p. 463; Schiff, Ann. d. Chem. (1889), 253, p. 236; Poulsson, Arch. f. Exp. Path. u. Pharm. (1895), 35, p. 97; Boehm, Ibid. (1897), 38, p. 35; Ann. d. Chem. (1898), 302, p. 171.

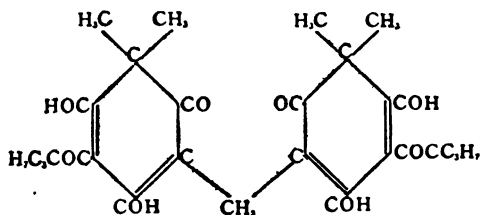
<sup>17</sup> Filix acid has also been isolated by Hausmann from *Athyrium Filix femina* Roth. Arch. d. Pharm. (1899), 237, p. 556, and has been identified by Bowman in *Aspidium rigidum* Swartz. Am. J. Pharm. (1881), 53, p. 389.

<sup>18</sup> Matsdorff, Apoth. Ztg. (1901), 16, p. 274.

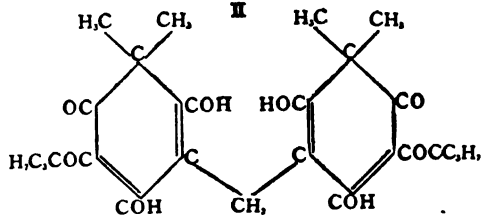
**Albaspidin.**<sup>19</sup> Albaspidin crystallizes in fine colorless needles melting at 147 to 148°C. It is readily soluble in ether, chloroform and benzol, difficultly soluble in alcohol, acetone and glacial acetic acid. Its constitution is stated to be represented by one of the three following formulae:<sup>20</sup>



I



II



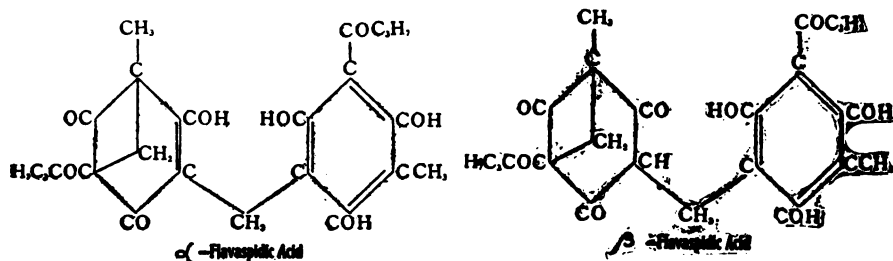
III

**Flavaspidic acid.** Flavaspidic acid ( $C_{24}H_{28}O_8$ ) was first isolated from the ethereal extract by Boehm. It is stated to exist in two forms ( $\alpha$  and  $\beta$ ) which differ in their melting points, the  $\alpha$ -flavaspidic acid melting at 92°C and the  $\beta$ -modification at 156°C. The  $\alpha$ -acid on heating is converted into the  $\beta$ -acid

<sup>19</sup> Albaspidin should not be confused with aspidin. Hausmann has shown the latter to be a constituent of *Dryopteris spinulosa* O. Kuntze, but that it is not present in *Dryopteris filix mas* Schott. Arch. d. Pharm. (1899), 237, p. 544.

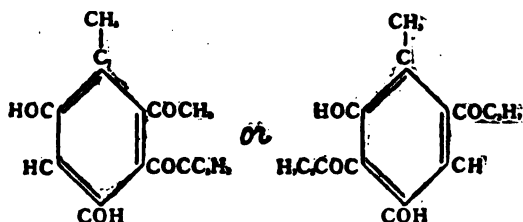
<sup>20</sup> Boehm, Arch. f. Exp. Path. u. Pharm. (1897), 38, p. 35; Ann. d. Chem. (1901), 318, p. 268.

which may be crystallized from hot benzol or glacial acetic acid. The  $\beta$ -form is converted into the  $\alpha$ -modification on crystallizing the former from alcohol. The  $\alpha$ -acid is thought to be the enol, the  $\beta$ -acid the keto-form. The structure is shown in the following formulae:<sup>21</sup>



Flavaspidic acid has been isolated from the male fern rhizome in quantities varying from 0.10 to 0.15 per cent.<sup>22</sup>

*Aspidinol.* Aspidinol ( $C_{12}H_{16}O_4$ ) crystallizes in small yellowish-white needles melting at 156 to 161°C. It is difficultly soluble in petroleum ether and benzol, readily soluble in ether, alcohol, chloroform, carbon disulphide and acetone. The following two formulae have been suggested by Boehm as representing the structure of this compound:<sup>23</sup>



*Flavaspidin.*<sup>24</sup> Flavaspidin closely resembles flavaspidic

<sup>21</sup> Boehm, Ann. d. Chem. (1901), 318, p. 253; Ibid. (1903, 329, p. 310.

<sup>22</sup> In addition to establishing the presence of flavaspidic acid in the male fern rhizome, Hausmann has also isolated this compound from *Athyrium Filix femina* Roth. and *Aspidium spinulosum* Swartz. Arch. d. Pharm. (1899), 237, p. 556.

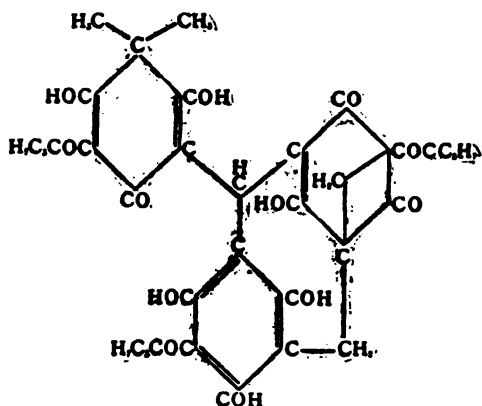
<sup>23</sup> Arch. f. Exp. Path. u. Pharm. (1893), 33, p. 35; Ann. d. Chem. (1901), 318, p. 245; Ibid. (1903), 329, p. 286.

<sup>24</sup> Kraft. Schweiz. Wochenschr. f. Chem. u. Pharm. (1902), 40, p. 323.

The "phloraspin" ( $C_{12}H_{16}O_4$ ) of Boehm is probably identical with flavaspidin. The pale yellow crystals obtained from the alcoholic solution melt at 211°C, and are stated to be almost insoluble in ether, petroleum ether, benzene and carbon disulphide, but more readily soluble in acetone, chloroform, hot absolute alcohol, ethyl acetate, glacial acetic acid and boiling xylene. Ann. d. Chem. (1903), 329, p. 338.

acid. It crystallizes from ethyl acetate in nearly colorless prisms melting at  $199^{\circ}\text{C}$ . It is soluble in methyl alcohol, difficultly soluble in ether, carbon disulphide and alcohol, readily soluble in warm benzene, chloroform, ethyl acetate, acetone and amyl alcohol.

*Filmaron*.<sup>25</sup> Filmaron ( $\text{C}_{47}\text{H}_{52}\text{O}_{16}$ ) is a light yellow, amorphous powder melting at about  $60^{\circ}\text{C}$ . It is insoluble in water, difficultly soluble in alcohol, methyl alcohol and petroleum ether, readily soluble in acetone, chloroform, ether, ethyl, acetate, benzene, carbon disulphide, carbon tetrachloride, amyl alcohol and glacial acetic acid. In acetone solution, at ordinary temperatures or upon warming with alcohol, it gradually decomposes into filix acid and filixnigrin. The following structural formula has been suggested by Kraft:



*Filixnigrin*.<sup>26</sup> Filixnigrin is the term used by Kraft to designate the mixture of brown to black amorphous decomposition products of the foregoing constituents. These decomposition products differ from the mother substances in that they are insoluble in petroleum ether. They have been isolated from the ethereal extract. To what extent they occur in the plant, if at all, has not been determined.

*Chlorophyll*. The green coloring matter of the male fern rhizome and of the oleoresin prepared therefrom is generally conceded by the various investigators to be chlorophyll, al-

<sup>25</sup> Kraft, l. c.

<sup>26</sup> Kraft, l. c.

though, no attempt appears to have been made to determine its composition. Work upon the pigments present in a closely related species of fern, *Aspidium Filix femina* Roth. has resulted in the isolation of carotin ( $C_{40}H_{56}O$ ) and three aspidiophylls,  $C_{208}H_{347}O_{32}N$ ,  $C_{240}H_{320}O_{31}N_2$  and  $C_{210}H_{346}O_{48}N_{20}$ .<sup>27</sup>

The amount of chlorophyll present in the rhizome varies with its age and with the season of the year.<sup>28</sup>

**Wax.** The wax occurring in the male fern rhizome has not been studied from a chemical standpoint, although its presence in the ethereal extract was observed at a very early date.<sup>29</sup>

**Filix Tannic Acid.**<sup>30</sup> Filix tannic acid ( $C_{41}H_{48}NO_{24}$ ) is a glucoside breaking down upon hydrolysis into hexose and a mixture of reddish-brown compounds.<sup>31</sup> It is readily soluble in water and dilute alcohol.

Filix tannic acid usually constitutes about 7 per cent. of the rhizome, as much as 7.8 per cent, having been isolated therefrom.<sup>32</sup>

**Ash.** Analyses<sup>33</sup> of the male fern rhizome have shown the ash to contain the basic elements, K, Na, Ca, Mg, Al and Fe combined with the acid radicles  $Cl'$ ,  $SO_4''$ ,  $PO_4'''$ ,  $SiO_3''$  and

<sup>27</sup> Ebard, Ann. Inst. Pasteur (1899), 13, p. 456. The more recent work of Willstaetter and his pupils on the chlorophylls isolated from more than 200 different plants belonging to numerous families indicates that magnesium is a constant constituent of the molecule, which is considered by them to be a methyl phytyl ester of the tricarboxylic acid, chlorophyllin,  $C_{55}H_{82}N_4Mg(COOH)_3$ . Viewed in this light, the above formulae for the aspidiophylls are erroneous in that they contain no magnesium and express molecular weights which are much too high. Ann. d. Chem. (1908), 358, p. 267; *Ibid.* (1910), 378, p. 1.

<sup>28</sup> Kruse has observed that the rhizomes collected in April and October have a more intense green color than those gathered in July. Arch. d. Pharm. (1876), 209, p. 24.

<sup>29</sup> Batso, Trommsdorff's n. Journ. d. Pharm. (1827), 14, p. 294; Peschier *Ibid.* (1828), 17, p. 5 and Bock, Arch. d. Pharm. (1851), 115, p. 266, report the presence of a stearin-like substance in the ethereal extract.

Caesar and Lorets have observed that rhizomes rich in wax yield an ethereal extract which is not fluid at the ordinary temperature. *Gecheafts Ber.* (1897), p. 62.

<sup>30</sup> In the light of our present knowledge concerning the chemistry of male fern, filix tannic acid is not considered to be a constituent of the oleoresin when prepared with ether. As its presence in the latter has been reported by early investigators, the above description has been included here. See analysis by Bock, Arch. d. Pharm. 1851, 115, p. 266.

<sup>31</sup> Malin, Ann. d. Chem. (1867), 115, p. 276; Wollenweber, Arch. d. Pharm. (1906), 244, p. 480.

<sup>32</sup> Wollenweber, l. c.

<sup>33</sup> Bock, Arch. d. Pharm. (1851), 115, p. 257; Spies, Jahresb. d. Pharm. (1860), 20, p. 15.

CO<sub>2</sub>". Hell and Company<sup>34</sup> report the presence of 0.0144 per cent. of copper. Spies, however, was unable to detect the presence of either copper or manganese.

The ash content of the dried rhizomes varies, about 2.0 to 3.0 per cent being the usual amount obtained.<sup>35</sup>

### *Constituents of Therapeutic Importance*

The value of the oleoresin of aspidium as a teniafuge has at various times been attributed to either its filix acid<sup>1</sup> or volatile oil<sup>2</sup> content. Comparatively recent pharmacological investigation,<sup>3</sup> however, has shown that the property of expelling the tape worm is not due to a single constituent, but is shared by a number of the acid-like components, namely: filix acid, flavaspidic acid, albaspidin, aspidinol, flavaspidinin and filmaron. Of these substances, filmaron is the most active and is stated by Jacquet<sup>4</sup> and others to be the constituent of most importance therapeutically.

The diminution in the therapeutic activity of the oleoresin on ageing has been found to be due to the breaking down of some of these constituents into compounds which are inert or less active as teniafuges. Of the decomposition products tested by Straub, phloroglucin, filicin acid and butyric acid were found to be non-toxic when administered to frogs.<sup>5</sup> Filix acid on the other hand was found to be toxic. Its value as a teniafuge is, however, doubtful.<sup>6</sup>

### *Physical Properties*

*Color:* The color of the oleoresin varies to a considerable extent depending principally on the condition of the drug from which it is prepared. It is described by various writers as being yellowish-green, green, dark green or greenish-brown.

<sup>34</sup> Pharm. Post (1894), 27, p. 168; Journ. de Pharm. et de Chim., 139, p. 493.

<sup>35</sup> Bock gives the ash content of the air dried rhizomes as 2.13 per cent., Kruse as 1.90 to 2.2 and Spies as 2.74. For the exsiccated rhizomes, the latter obtained 3.19 per cent.

<sup>1</sup> Poulsson, Arch. f. Exp. Path. u. Pharmak. (1891), 29, p. 9.

<sup>2</sup> Kobert, Therap. Monatsch. (1893), p. 136.

<sup>3</sup> Straub, Arch. f. Exp. Path. u. Pharmak. (1902), 48, pp. 1-47.

<sup>4</sup> Therap. Monatsch. (1904), 18, p. 391.

<sup>5</sup> *l. c.*

<sup>6</sup> Boehm, Arch. f. Exp. Path. u. Pharmak. (1897), 38, p. 35.

When prepared from the freshly dried and powdered rhizomes gathered in the autumn,<sup>1</sup> it usually has an olive-green color when spread out in a thin layer on a white porcelain surface. A brownish-green color is an indication of the use of old deteriorated drug<sup>2</sup> in its preparation, whereas, a deep green color suggests adulteration with salts of copper or chlorophyll.<sup>3</sup>

The nature of the solvent employed in extracting the drug is also stated to have an influence on the color of the preparation, the use of ether (specific gravity 0.720) yielding an oleoresin of a green color, whereas, the color is brownish-green when ether (specific gravity 0.728) is employed.<sup>4</sup>

*Odor:* The odor of the oleoresin is peculiar, like that of male fern.

*Taste:* The preparation has a bitter, nauseous, subacid taste.

*Consistence:* The oleoresin when freshly prepared is homogeneous and is of about the same degree of fluidity as castor oil. It is variously stated as being of the consistence of syrup, fresh honey or an oily extract.

*Solubility:* The oleoresin when prepared with ether forms clear or slightly cloudy solutions with acetone, ether, chloroform and carbon disulphide.<sup>5</sup> It is partially soluble in carbon tetrachloride, benzene, methyl alcohol, ethyl alcohol (95 per cent.), glacial acetic acid and petroleum ether. The degree to which it is soluble in the last three solvents mentioned has been made the basis of tests for the detection of adulteration with castor oil.

According to Hill (1913), not less than 8 volumes of the oleoresin should be soluble in 10 volumes of petroleum ether, a lesser degree of solubility indicating adulteration. Jehn and

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<sup>1</sup> The oleoresin prepared from rhizomes gathered in October is stated by Kruse (1876) to have a more intense green color than that prepared from rhizomes gathered in July.

Caesar and Loretz in their *Berichte* for 1913 state the condition of the season in which the rhizomes are harvested has an influence on their color, which becomes evident in the oleoresin, *e. g.* the oleoresin, when prepared from the rhizomes gathered in a dry season, is often very dark green in color.

<sup>2</sup> Buchner (1826) found that when the drug was kept in an open container for more than a year a brown instead of a green colored oleoresin was obtained.

<sup>3</sup> Wepen and Lueders (1892), Beckurts and Peters (1893) and others.

<sup>4</sup> Bellingrodt. (1898).

<sup>5</sup> This statement holds good only for the freshly prepared oleoresin and does not apply when the same contains deposited material.



Crato<sup>1</sup> state that the presence of castor oil is indicated when more than 50 per cent. of the oleoresin is soluble in 95 per cent. alcohol. Solubility tests made in the laboratory with glacial acetic acid have shown that not over 10 per cent. by volume of the oleoresin is soluble in the latter, a greater degree of solubility indicating adulteration with castor oil.

*Specific gravity:* Observations made in the laboratory show that the specific gravity should be above 1.000 when determined at 25°C. This is in keeping with the findings of Parry (1911) and Hill (1913), respectively, even though their determinations were made at 15°C. It is also the standard given in the late edition of the British Pharmacopoeia. A specific gravity of less than 1.000 usually indicates adulteration with castor oil or a preparation naturally low in filicin content. It may, however, be due to the addition of chlorophyll as pointed out by Hill, or to the presence of unevaporated solvent. These details, together with the effect produced by the use of different solvents in the extraction of the drug are brought out in the following tables:

TABLE 13.—*Specific gravities of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Specific gravity
				At 25° C
1.....	1910...	DuMez & Netzel .....	Alcohol.....	1.166
2.....	"	" .....	Acetone.....	1.052
3.....	"	" .....	Ether.....	1.012
4.....	"	" .....	Petrol. ether.....	0.995
1.....	"	DuMez.....	Acetone.....	1.048
2.....	"	" .....	Ether.....	1.000
1.....	1916...	" .....	Acetone.....	1.009 (?)
2.....	"	" .....	Ether.....	0.997 (?)

<sup>1</sup> *Kommentar zum Arzneibuch fuer das deutsche Reich* (1901), p. 258.

<sup>2</sup> Same as 2 and 3 after having stood in the laboratory for 6 years. Both contained a heavy deposit which was not mixed with the liquid portion when the specific gravity was redetermined.

TABLE 14.—*Specific gravities of commercial samples.*

Sample No.	Date	Observer	Source	Specific gravity
				At 15° C
1	1911	Parry	Not given	0.973 <sup>(1)</sup>
2	"	"	"	0.973 <sup>(1)</sup>
3	"	"	"	0.974 <sup>(1)</sup>
4	"	"	"	0.975 <sup>(1)</sup>
5	"	"	"	0.975 <sup>(1)</sup>
6	"	"	"	0.983 <sup>(1)</sup>
1	1912	Southall Bros. & Barclay	"	0.9745 <sup>(1)</sup>
2	"	"	"	0.9800 <sup>(1)</sup>
3	"	"	"	1.0148
4	"	"	"	1.0200
5	"	"	"	1.0205
6	"	"	"	1.0281
				Temp. <sup>(2)</sup>
1	1913	Bohrisch	German firms	0.9886 <sup>(3)</sup>
2	"	"	"	0.9842 <sup>(3)</sup>
3	"	"	"	0.9888 <sup>(3)</sup>
4	"	"	"	1.0109
				At 25° C
1	1913	DuMez	Manila, P. I.	0.977 <sup>(3)</sup>
2	"	"	England	0.985 <sup>(1)</sup>
3	"	"	"	0.9889 <sup>(1)</sup>
4	"	"	United States	1.001
5	"	"	Germany	1.003
6	"	"	England	1.003 <sup>(1)</sup>
7	"	"	United States	1.008 <sup>(3)</sup>
8	"	"	Germany	1.008
				At 15° C
1	1913	Harrison & Self	Germany	0.987 <sup>(4)</sup>
2	"	"	"	0.997
3	"	"	"	1.015
4	"	"	"	1.020
5	"	"	"	1.029
6	"	"	"	1.029
1	"	Hill	Europe	0.9829 <sup>(3)</sup>
2	"	"	"	0.9850
3	"	"	"	0.9921
4	"	"	"	0.9944
5	"	"	"	0.9980 <sup>(3)</sup>
6	"	"	"	0.9980 <sup>(1)</sup>
7	"	"	England	0.9985 <sup>(1)</sup>
8	"	"	"	1.000
9	"	"	"	1.000
10	"	"	"	2.0006 <sup>(1)</sup>
11	"	"	"	1.0038
12	"	"	"	1.0045
13	"	"	"	1.0065
14	"	"	"	1.0075
15	"	"	England	1.0090
16	"	"	Europe	1.0109
17	"	"	"	1.0179
18	"	"	"	1.0190
19	"	"	"	1.0227
20	"	"	England	1.0233
21	"	"	Europe	1.0235
22	"	"	"	1.0240
23	"	"	"	1.0249
1	"	Southall Bros. & Barclay	Not given	1.025
2	"	"	"	1.025
1	1915	"	"	0.9985
2	"	"	"	1.0110
3	"	"	"	1.021
4	"	"	"	1.023
5	"	"	"	1.030
				At 25° C
1	1916	DuMez	Squibb & Sons	0.9808 <sup>(3)</sup>
2	"	"	Lilly & Co.	0.9947 <sup>(3)</sup>
3	"	"	Parke, Davis & Co.	1.0103
4	"	"	Stearns & Co.	1.0379 <sup>(3)</sup>

<sup>1</sup> Adulterated with castor oil.<sup>2</sup> Contained added chorophyll.<sup>3</sup> Low in crude filicin content.<sup>4</sup> Referred to as suspicious.<sup>5</sup> Contained ether.

**Refractive index:** A refractive index of not less than 1.490 at 40°C is required for this oleoresin by the late edition of the British Pharmacopoeia. This is in accordance with the observations of Hill (1913). The statement by Parry (1911), that the refractive index should not be below 1.500 when determined at 20°C is confirmed by the results which were obtained by Harrison and Self (1913), and is more in conformity with the observations made in this laboratory at 25°C. When the oleoresin is properly prepared, ether being the menstruum used, the refractive index appears to vary directly as the crude filicin content. A low refractive index, therefore, indicates a preparation naturally low in filicin content. With respect to the commercial oleoresins, however, a low refractive index may also result from adulteration with castor oil or chlorophyll, or may be due to the presence of unevaporated solvent as is shown in the tables which follow:

TABLE 15.—*Refractive indices of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Refractive index
1.....	1913	DuMez.....	Ether.....	At 25° C 1.500
1.....	"	Harrison & Self.....	".....	At 20° C 1.4995
2.....	"	".....	".....	1.5018
3.....	"	".....	".....	1.5086
4.....	"	".....	".....	1.5088
5.....	"	".....	".....	1.5088
6.....	"	".....	".....	1.5102
7.....	"	".....	".....	1.5120
8.....	"	".....	".....	1.5122
9.....	"	".....	".....	1.5126
10.....	"	".....	".....	1.5145
11.....	"	".....	".....	1.5157
1.....	1916	DuMez.....	Acetone.....	1.500 <sup>1</sup>
2.....	"	".....	Ether.....	1.498 <sup>1</sup>

<sup>1</sup> These figures represent the refractive indices of oleoresins which had stood in the laboratory for six years.

TABLE 16—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
1.....	1911	Evans Sons, Lescher & Webb	Not stated .....	At 15° C 1.484 <sup>(?)</sup>
2.....	"	"	"	1.485 <sup>(?)</sup>
3.....	"	"	"	1.501
4.....	"	"	"	1.501
1.....	"	Parry.....	"	At 20° C 1.484 <sup>(1)</sup>
2.....	"	"	"	1.484 <sup>(1)</sup>
3.....	"	"	"	1.487 <sup>(1)</sup>
4.....	"	"	"	1.488 <sup>(2)</sup>
5.....	"	"	"	1.4885 <sup>(1)</sup>
6.....	"	"	"	1.493 <sup>(1)</sup>
1-16....	1912	Evans Sons, Lescher & Webb	"	At 15° C 1.507 to 1.509
1.....	"	Southall Bros. & Barclay .	"	At 20° C 1.4830 <sup>(1)</sup>
2.....	"	"	"	1.4840 <sup>(1)</sup>
3.....	"	"	"	1.5040
4.....	"	"	"	1.5055
5.....	"	"	"	1.5085
6.....	"	"	"	1.5210(?)
1.....	1913	DuMez.....	England.....	At 25° C 1.484 <sup>(1)</sup>
2.....	"	"	"	1.485 <sup>(1)</sup>
3.....	"	"	Manila, P. I .	1.489
4.....	"	"	United States.....	1.480
5.....	"	"	"	1.480
6.....	"	"	Germany.....	1.492
7.....	"	"	England.....	1.488
8.....	"	"	Germany.....	1.494
1.....	"	Harrison & Self.....	Germany.....	At 26° C 1.4910 <sup>(2)</sup>
2.....	"	"	"	1.4944
3.....	"	"	"	1.4984
4.....	"	"	"	1.5055
5.....	"	"	"	1.5080
6.....	"	"	"	1.5084
1.....	"	Hill.....	Europe.....	At 40° C 1.4823 <sup>(1)</sup>
2.....	"	"	"	1.4869 <sup>(1)</sup>
3.....	"	"	"	1.4874 <sup>(1)</sup>
4.....	"	"	"	1.4880
5.....	"	"	"	1.4900
6.....	"	"	"	1.4915 <sup>(2)</sup>
7.....	"	"	"	1.4920
8.....	"	"	England.....	1.4922
9.....	"	"	Europe.....	1.4925
10.....	"	"	"	1.4935
11.....	"	"	"	1.4940
12.....	"	"	"	1.4945
13.....	"	"	England.....	1.4960
14.....	"	"	"	1.4965
15.....	"	"	Europe.....	1.4980
16.....	"	"	"	1.4985
17.....	"	"	"	1.4988
18.....	"	"	"	1.4990
19.....	"	"	"	1.5006
20.....	"	"	"	1.5025
21.....	"	"	"	1.5036
1-7.....	"	Evans Sons, Lescher & Webb	Not stated.....	At 15° C 1.500 to 1.510
8.....	"	"	"	1.495 <sup>(2)</sup>
9.....	"	"	"	1.497 <sup>(2)</sup>
10.....	"	"	"	1.499 <sup>(2)</sup>
1.....	"	Southall Bros. & Barclay .	"	At 25° C 1.4975
2.....	"	"	"	1.5115
1.....	1915	Southall Bros. & Barclay .	"	1.4976
2.....	"	"	"	1.4983
3.....	"	"	"	1.5000
4.....	"	"	"	1.5001
5.....	"	"	"	1.5020
1.....	1916	DuMez.....	Stearns & Co.....	At 25° C 1.4953 <sup>(4)</sup>
2.....	"	"	Lilly & Co.....	1.4983 <sup>(4)</sup>
3.....	"	"	Sculbb & Sons.....	1.4993 <sup>(4)</sup>
4.....	"	"	Parke, Davis & Co.....	1.4998

<sup>1</sup> Samples adulterated with castor oil.<sup>2</sup> Samples contained added chlorophyll.<sup>3</sup> Samples are referred to as being suspicious.<sup>4</sup> Low in crude filicin content.<sup>5</sup> Contained unevaporated solvent.

*Chemical Properties.*

*Loss in weight on heating:* Hill (1913) stated that the oleoresin when heated at 100°C should not lose more than 6 per cent. of its weight, a greater loss indicating the presence of unevaporated solvent. The statement is confirmed by other data of this nature reported in the literature as well as by the results obtained in the laboratory as is shown in the tables which follow:

TABLE 17—*Laboratory preparations—Loss in weight on heating.*

Sample No.	Date	Observer	Solvent	Per cent of loss on heating
1.....	1887	Kremel.....	Alcohol.....	At 100° C
2.....	"	".....	Ether.....	17.40
1.....	1904	Dieterich.....	".....	0.70
				4.51
1.....	1916	DuMez.....	Acetone.....	At 110°
2.....	"	".....	Ether.....	2.51 C
				2.37

TABLE 18.—Commercial oleoresins—Loss in weight on heating.

Sample No.	Date	Observer	Source	Per cent. of loss on heating
				At 100° C
1.....	1891	Dieterich.....	Germany.....	2.70
1.....	1893	".....	".....	1.15
2.....	"	".....	".....	1.60
3.....	"	".....	".....	1.75
1.....	1894	".....	".....	1.90
2.....	"	".....	".....	2.32
3.....	"	".....	".....	3.65
1.....	1895	".....	".....	1.75
1.....	1896	".....	".....	1.62
1.....	1897	".....	".....	4.52
2.....	"	".....	".....	4.72
1.....	1901	".....	".....	5.23
1.....	1903	".....	".....	5.52
2.....	"	".....	".....	7.38
1.....	1904	".....	".....	2.96
2.....	"	".....	".....	3.09
1.....	1905	".....	".....	5.06
2.....	"	".....	".....	7.51
1.....	1913	Hill.....	Europe.....	2.43
2.....	"	".....	".....	2.44
3.....	"	".....	England.....	2.57
4.....	"	".....	Europe.....	2.89
5.....	"	".....	".....	3.35
6.....	"	".....	".....	3.63
7.....	"	".....	".....	3.65
8.....	"	".....	".....	4.23
9.....	"	".....	".....	4.40
10.....	"	".....	".....	4.57
11.....	"	".....	".....	4.84
12.....	"	".....	".....	4.84
13.....	"	".....	England.....	5.03
14.....	"	".....	Europe.....	5.22
15.....	"	".....	".....	6.50 <sup>(1)</sup>
16.....	"	".....	".....	6.52 <sup>(1)</sup>
17.....	"	".....	".....	6.60 <sup>(1)</sup>
18.....	"	".....	".....	6.68 <sup>(1)</sup>
				At 100 to 105° C
1.....	1914	Linke.....	Brückner, Lampe & Co....	3.20
2.....	"	".....	Caesar & Loretz.....	3.25
3.....	"	".....	Merck & Co.....	6.85
				At 110° C
1.....	1916	DuMaz.....	Parke, Davis & Co.....	1.75
2.....	"	".....	Stearns & Co.....	2.03
3.....	"	".....	Lilly & Co.....	6.01
4.....	"	".....	Squibb & Sons.....	7.13 <sup>(1)</sup>

(1) Unevaporated solvent (ether) was present.

**Ash Content:** The results of this nature reported in the literature, as well as those obtained in the laboratory, indicate that the ash content of the oleoresin, when prepared with ether, seldom exceeds 0.50 per cent, which is the standard given in the Belgian and Spanish pharmacopœias. With respect to the commercial samples examined in the laboratory, the high ash content obtained was due to the presence of copper, evidently a result of the use of copper utensils in the manufacture of these preparations. The results of the determinations made in the

laboratory and those reported in the literature are given in the tables which follow:

TABLE 19.—*Ash contents of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Per cent of ash.
1.....	1904	Dieterich.....	Ether.....	0.36
1.....	1916	DuMez.....	Ether.....	0.26
2.....			Acetone.....	0.51

TABLE 20.—*Ash contents of commercial oleoresins.*

Sample No.	Date	Observer	Source	Per cent of ash	Foreign constituents
1.....	1891	Dieterich.....	Germany.....	0.40	
1.....	1893	".....	".....	0.45	
2.....	"	".....	".....	0.50	
3.....	"	".....	".....	0.50	
1.....	1894	".....	".....	0.42	
2.....	"	".....	".....	0.50	
3.....	"	".....	".....	0.55	
1.....	1895	".....	".....	0.50	
1.....	1896	".....	".....	0.45	
1.....	1897	".....	".....	0.43	
2.....	"	".....	".....	0.52	
1.....	1901	".....	".....	0.32	
1.....	1903	".....	".....	0.27	
2.....	"	".....	".....	0.30	
3.....	"	".....	".....	0.30	
1.....	1904	".....	".....	0.33	
2.....	"	".....	".....	0.33	
1.....	1905	".....	".....	0.26	
2.....	"	".....	".....	0.46	
1.....	1914	Linke.....	Brueckner, Lampe & Co.....	0.34	Copper
2.....	"	".....	Caesar & Loretz.....	0.41	
3.....	"	".....	Riedel.....	0.52	"
4.....	"	".....	Merck & Co.....	0.53	
1.....	1916	DuMez.....	Lilly & Co.....	0.53	Copper
2.....	"	".....	Squibb & Sons.....	0.54 <sup>(1)</sup>	
3.....	"	".....	Parke, Davis & Co.....	0.30	"
4.....	"	".....	Stearns & Co.....	0.32	"

(<sup>1</sup>) Contained unevaporated solvent—ether.

*Acid number:* The acid numbers 82.2 and 82.7 were obtained for the oleoresins prepared in the laboratory. Inasmuch, however, as these preparations were made six years previous to the time when the determinations were made, it is thought that the value of this constant would be somewhat lower for the oleoresin when freshly prepared. This statement is based on the assumption that the acidity of the preparation will increase on standing due to the partial hydrolysis of the glycerides of the fatty acids and to the breaking down of the complex substances constituting the so-called crude flicin.

In the case of the commercial samples, the acid numbers were found to vary as a rule in the same direction as the filicin content. It would appear, therefore, that the value obtained for this constant might serve as a check on the latter determination. The results obtained in the determination of the acid numbers of the preparations examined in the laboratory and those reported by Kremel follow:

TABLE 21.—*Acid numbers of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Acid number
1.....	1887	Kremel .....	Alcohol .....	23
1.....	1916	DuMez.....	Ether .....	50 to 70
2.....				82.7 <sup>(1)</sup>
2.....			Acetone.....	82.2 <sup>(1)</sup>

(<sup>1</sup>) These preparations were 6 years old when the acid number was determined.

TABLE 22.—*Acid numbers of commercial oleoresins.*

Sample No.	Date	Observer	Source	Acid Number
1.....	1916	DuMez.....	Stearns & Co.....	50.2
2.....	"	" .....	Squibb & Sons.....	65.9 <sup>(1)</sup>
3.....	"	" .....	Lilly & Co.....	72.9
4.....	"	" .....	Parke, Davis & Co.....	87.8

(<sup>1</sup>) Contained ether.

*Saponification value:* Determinations made by Parry in 1911 lead him to state that the saponification value of this preparation should not be lower than 230, corresponding to a crude filicin content of not less than 22 per cent. The values obtained for this constant in the laboratory and those reported by Harrison and Self agree, as a rule with this statement, when the minimum filicin content is taken as 20 per cent. A value of less than 230 in the case of commercial samples has been shown to be due in general to adulteration with castor oil. In a few instances, however, it is to be attributed to the presence of unevaporated solvent, or to a low filicin content due to the use of a poor quality of drug in the manufacture of the oleoresin.



The relatively high values obtained in the laboratory for the old preparations low in filicin content (16.0 and 16.27 per cent, respectively) is very likely due to the effect caused by the hydrolysis of the constituents of high molecular weight with the formation of acids of comparatively low molecular weight.<sup>1</sup> The saponification values found for the preparations examined in the laboratory as well as those reported in the literature are given in the tables which follow:

TABLE 23 — *Saponification values of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Saponification value
1-20.....	1887	Kremel.....	Ether.....	116 to 165
1.....	1911	Parry.....	.....	230 to 250
2.....	1913	DuMez.....	Acetone.....	208.8
1.....	"	".....	Ether.....	229.3
2.....	"	Harrison & Self.....	.....	225.0
3.....	"	".....	".....	227.0
4.....	"	".....	".....	236.5
5.....	"	".....	".....	248.0
6.....	"	".....	".....	248.9
7.....	"	".....	".....	251.5
8.....	"	".....	".....	252.0
9.....	"	".....	".....	254.5
10.....	"	".....	".....	255.0
11.....	"	".....	".....	259.0
1.....	1916	DuMez.....	Acetone.....	245.2 <sup>(1)</sup>
2.....	"	".....	Ether.....	246.4 <sup>(1)</sup>

<sup>(1)</sup> Old preparations low in filicin content.

<sup>1</sup> See under "Chemistry of the drug and oleoresin."

TABLE 24—*Saponification values of commercial oleoresins.*

Sample No.	Date.	Observer.	Source.	Saponification value
1.....	1904	Dieterich .....	Germany .....	204.4
2.....		" .....	" .....	234.2
1.....	1911	Evans Sons, Lescher & Webb .....	Not given.....	195.2 (1)
2.....	"	" .....	" .....	220.4
3.....	"	" .....	" .....	248.8
1.....	"	Parry .....	" .....	187.0 (1)
2.....	"	" .....	" .....	200.0 (1)
3.....	"	" .....	" .....	207.0 (1)
4.....	"	" .....	" .....	208.0 (1)
5.....	"	" .....	" .....	210.0 (1)
6.....	"	" .....	" .....	221.0 (1)
1.....	1912	Southall Bros. & Barclay .....	" .....	195.1 (1)
2.....	"	" .....	" .....	204.6 (1)
3.....	"	" .....	" .....	235.4
4.....	"	" .....	" .....	241.0
5.....	"	" .....	" .....	250.3
6.....	"	" .....	" .....	253.2
1.....	1913	DuMez .....	England .....	195.7 (1)
2.....	"	" .....	Manila, P. I. ....	200.3 (2)
3.....	"	" .....	England .....	202.4 (1)
4.....	"	" .....	United States .....	206.7 (2)
5.....	"	" .....	England .....	208.7 (1)
6.....	"	" .....	Germany .....	214.6 (2)
7.....	"	" .....	" .....	225.5
8.....	"	" .....	United States .....	240.5
1.....	"	Harrison & Self .....	Germany .....	205.0 (2)
2.....	"	" .....	" .....	213.0
3.....	"	" .....	" .....	218.0
4.....	"	" .....	" .....	223.0
5.....	"	" .....	" .....	225.0
6.....	"	" .....	" .....	237.0
1.....	"	Southall Bros. & Barclay .....	Not given.....	225.1
2.....	"	" .....	" .....	263.1
1.....	1915	" .....	" .....	206.5
3.....	"	" .....	" .....	236.0
3.....	"	" .....	" .....	250.0
4.....	"	" .....	" .....	253.1
5.....	"	" .....	" .....	254.6
1.....	1916	DuMez .....	Stearns & Co.....	190.0 (2)
2.....	"	" .....	Lilly & Co. ....	211.4 (2)
3.....	"	" .....	Squibb & Sons .....	233.2 (1)
4.....	"	" .....	Parke, Davis & Co.....	249.1

<sup>1</sup> Adulterated with castor oil.<sup>2</sup> Low in crude filicin content.<sup>3</sup> Referred to as suspicious.<sup>4</sup> Contained ether.

*Iodine value:* Observations made in the laboratory indicate that the oleoresin should have an iodine value of not less than 99, corresponding to at least 20 per cent. of crude filicin. Preparations giving a lower value than this were found to be low in crude filicin content due to adulteration with castor oil or to the presence of unevaporated solvent. On the other hand, it was observed that a high iodine value does not always signify a high filicin content, *e. g.* iodine values of 106.3 and 108.1 were obtained for preparations containing only 16.0 and 16.27 per cent. of crude filicin, respectively. As the latter were

old and contained deposited material equal to nearly one-half of their bulk, the high iodine values obtained for the supernatant liquid portions were very likely due to the concentration of the compounds of a lesser degree of saturation (glycerides of the unsaturated fatty acids) as a result of the decomposition and deposition of the more highly saturated compounds (crude filicin). The results obtained in the determination of this constant are shown in the following tables:

TABLE 25.—*Iodine values of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Iodine value
1.....	1911	Evans Sons, Lescher & Webb.....	Ether.....	101.8
1.....	1913	DuMez.....	Acetone.....	95.3
2.....	1913	".....	Ether.....	99.8
1.....	1916	".....	Acetone.....	106.3 <sup>(1)</sup>
2.....	1916	".....	Ether.....	108.1 <sup>(1)</sup>

<sup>1</sup> These preparations were six years old when examined.

TABLE 26.—*Iodine values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Iodine value
1.....	1804	Dieterich.....	Germany.....	100.6
2.....	"	".....	".....	84.2
1.....	1911	Evans Sons, Lescher & Webb.....	Not given.....	89.2 <sup>(1)</sup>
2.....	"	".....	".....	92.5 <sup>(1)</sup>
3.....	"	".....	".....	95.9
4.....	"	".....	".....	99.1
1.....	1913	DuMez.....	England.....	85.8 <sup>(1)</sup>
2.....	"	".....	Manila, P. I.....	87.2 <sup>(2)</sup>
3.....	"	".....	England.....	89.4 <sup>(1)</sup>
4.....	"	".....	United States.....	94.4
5.....	"	".....	Germany.....	97.1
6.....	"	".....	England.....	98.3 <sup>(1)</sup>
7.....	"	".....	Germany.....	100.2
8.....	"	".....	United States.....	101.5
1.....	1916	".....	Sculbb & Sons.....	95.3 <sup>(2)</sup>
2.....	"	".....	Stearns & Co.....	97.7 <sup>(2)</sup>
3.....	"	".....	Lilly & Co.....	98.2 <sup>(2)</sup>
4.....	"	".....	Parke, Davis & Co.....	103.2

<sup>1</sup> Adulterated with castor oil.

<sup>2</sup> Low in crude filicin content.

<sup>3</sup> Contained ether.

### Other Properties

The oleoresin, when freshly prepared, is homogeneous, but upon standing, a deposit is formed therein as a result of the breaking down of some of its constituents. The precipitated

material has been identified by Boehm<sup>1</sup> as crystalline filix acid and a wax-like substance. Kraft,<sup>2</sup> in a later investigation, confirmed the findings of Boehm insofar as they concerned the presence of filix acid. The wax-like material, however, he found to be composed of a number of substances, decomposition products of the therapeutically active constituents, which he designated as filixnigrin. As the deposit has been found to be active<sup>3</sup> in the expulsion of tapeworm, although in a much lesser degree than the oleoresin proper, the *United States Pharmacopæia* directs that it be mixed with the liquid portion before dispensing.

### *Special Qualitative Tests*

A number of the European pharmacopœias prescribe tests for the determination of the quality of this preparation. These tests are of two kinds, namely, those which have for their object the establishment of the presence of the constituents of therapeutic value, i. e. the substances of an acid character known collectively as crude filicin, and those which serve to identify starch when present. The former are based on the fact that the above mentioned constituents of an acid character may be precipitated directly by means of certain solvents, or from alkaline solutions by means of acids. The following are the official tests of this nature:

#### *Tests for Filicin.*

*Austrian Pharmacopœia (1906):* Upon adding an excess of petroleum ether to the oleoresin dissolved in a small quantity of ethyl ether, a white precipitate should be produced.

*Netherlands Pharmacopœia (1905):* If 0.025 gram of the oleoresin dissolved in 2 cubic centimeters of ether be shaken with 5 cubic centimeters of a saturated barium hydroxide solution and 5 cubic centimeters of water, the aqueous portion, when separated and filtered, should give a flocculent precipitate on being acidified with hydrochloric acid.

*Hungarian Pharmacopœia (1909):* If 0.25 gram of the extract be dissolved in 2 cubic centimeters of ether and shaken with 10 cubic centimeters of lime water, the aqueous portion filtered and acidified with hydrochloric acid, a copious white precipitate should be formed.

<sup>1</sup> Arch. f. exp. Path. u. Pharmak. (1897), 38, p. 35.

<sup>2</sup> Kraft (1902).

<sup>3</sup> Reuter, Pharm. Ztg. (1891), 36, p. 245; Straub, Arch. f. exp. Path. u. Pharmak. (1902), 48, p. 1.

The application of these tests in the laboratory has shown that they are of practically no value as an indication of the quality of the oleoresin, as preparations very low in crude filicin content give comparatively heavy precipitates when treated as described above. Furthermore, they do not serve as a means of identification as oleoresins prepared from the rhizomes of certain other species of fern<sup>1</sup> behave in a similar manner when subjected to these conditions.

### *Tests for Starch*

A test for the presence of starch has been included in those pharmacopœias in which the oleoresin is directed to be prepared by the process of maceration, namely, the German and Japanese. In these instances, it serves as a means of distinguishing between preparations which have been filtered as officially directed and those which have been merely strained through cloth as is often the case. A similar test is also found in the pharmacopœias of those countries (Hungary, Spain and Switzerland) in which this preparation is frequently made by maceration, although the official process is that of percolation. The test as officially recognized in the different countries is identical with that described in the German Pharmacopœia. It is as follows:

The oleoresin, when diluted by shaking with glycerin, should not show the presence of starch grains under the microscope.

Experience in the application of this test to the preparations examined in the laboratory has shown that it is unsatisfactory when carried out as described above. The fault lies in the fact that the glycerin cannot be thoroughly mixed with the oleoresin by shaking. If mixing is effected by trituration in a mortar, the results are better, although there is considerable danger in rupturing the starch grains by this procedure.

In addition to the foregoing, special tests have been proposed for the detection of adulterants when present. They are as follows:

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<sup>1</sup> See under "Drug used, its collection, preservation, etc."

*Tests for the Presence of the Oleoresin of Dryopteris Spinulosa.*

Hausmann found that the male fern of commerce frequently contained large quantities of the rhizomes of *Dryopteris spinulosa* Kunze. He therefore devised a test for the detection of the use of the latter in the preparation of the oleoresin. It is based on the fact that the rhizomes of *Dryopteris spinulosa* Kunze contain aspidin, whereas those of the official species, *Dryopteris Filixmas* Schott do not.

*Hausmann's Method (1899):* Dissolve a small amount of crude filicin<sup>1</sup> in as small a quantity of absolute ether as possible and set the solution aside in a desiccator. If aspidin is present, the thick solution will form a crystalline brine in a few hours, when the needle-like crystals of the former can easily be identified under the microscope. If aspidin is not present, the solution undergoes no change even on long standing except to deposit a granular substance.

*Tests for the Presence of Castor Oil*

The tests for the presence of castor oil are based on the solubility of the oleoresin in various solvents and are discussed under the heading, "Solubility."

*Tests for the Presence of Salts of Copper*

The tests for the presence of salts of copper involve an examination of the ash of the oleoresin and are discussed under the general treatment of the subject, "Ash content."

*Special Quantitative Tests.*

A great deal of work has been done with reference to the evaluation of this preparation, and as a result, a number of methods for the quantitative estimation of the constituents of therapeutic importance has been devised. The chemical methods may be conveniently divided into two groups, the one including those methods which have for their object the quantitative determination of the filix acid; and the other comprising the methods in which the quantity of the total constituents of an acid character is determined.

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<sup>1</sup> See under "Special quantitative methods".

*Methods for the Determination of Flix Acid.*

As the oleoresin was originally thought to owe its teniafuge properties to its flix acid content, the determination of this constituent naturally received consideration first. The nature of the methods devised for its estimation and their subsequent development is illustrated in the descriptions which follow:

*Method of Kremel (1887):* Place a weighed quantity (about 10 grams) of the oleoresin in a flask and macerate it successively with several portions of petroleum ether when the greater part will be dissolved leaving the flix acid as an insoluble residua. Collect the latter on a filter and wash with more petroleum ether. Then dissolve it while on the filter in hot alcohol, remove the latter by evaporation and again wash with petroleum ether to remove the last traces of fat. Finally dry and weigh.

*Method of Bocchi (1896):*<sup>1</sup> Dissolve 1 to 2 grams of the oleoresin in a small quantity of ether, place the solution in a separatory funnel and shake it with successive portions of lime water until the shakings become colorless and remain clear on the addition of acetic or hydrochloric acids. Filter the united lime water solutions into a separatory funnel and acidify with hydrochloric acid when a dirty yellow precipitate will form. Dissolve the latter by shaking with carbon disulphide added in successive portions, unite the shakings, filter and remove the solvent by evaporation on a water bath. Dry and weigh the residue which is pure flix acid.

*Method of Kraft (1896):* Add a solution composed of 2 grams of potassium carbonate, 40 grams of water and 60 grams of alcohol (95 per cent.) to 5 grams of the oleoresin in a suitable flask and shake for 15 minutes. Filter 83 grams of this liquid into a separatory funnel, add 9 grams of dilute hydrochloric acid, 50 grams of ether and 35 grams of water and shake vigorously. After the mixture has separated draw off the lower hydro-alcoholic liquid and repeat the shaking, using 35 grams more of water. Separate the latter and run the remaining ethereal solution into a tared Erlenmeyer flask of 100 cubic centimeters capacity. Distill off the greater part of the ether and evaporate the remainder down to about 2 grams. Dissolve the dried mass in 1.5 grams of amyl alcohol and precipitate the flix acid by the addition of 30 cubic centimeters of methyl alcohol (5 cubic centimeters added at once and the remainder drop by drop.) Allow the precipitate and supernatant liquid to stand over night in a cool place, then collect the former on a tared filter and wash it with 15 cubic centimeters of methyl alcohol (use 3 portions of 5 cubic centimeters.) Finally, dry the precipitate at a temperature between 60° and 70°C and weigh. The weight obtained will represent the flix acid contained in 4 grams of the oleoresin.

<sup>1</sup>The procedure as outlined above really gives the amount of total acid substances (crude flicin) present, but is described here as it was proposed by its originator as a method for the determination of the flix acid content.

*Original Method of Fromme (1896):* Dissolve 1.5 to 2 grams of the oleoresin in 2 grams of ether, and thoroughly mix the solution in a porcelain dish (diameter 8 to 10 centimeters) with 3 grams of calcined magnesia (or 8 grams of burned lime.) Allow the ether to evaporate completely and triturate the remaining dry pulverent mass with water, added gradually until a thin brine is formed. Set the mixture aside until the magnesia has settled, then decant the supernatant aqueous portion on a dry filter. Continue to repeat this operation, using fresh portions of water, until the filtrate no longer gives a precipitate when acidified with hydrochloric acid. Place the combined filtrates (usual weight 200 to 250 grams) in a separatory funnel, acidify with hydrochloric acid and shake out the precipitate with carbon disulphide added in successive portions (20, 10 and 10 cubic centimeters.) Filter the united carbon disulphide shakings into a round-bottom flask of 100 cubic centimeters capacity and evaporate to dryness on a water bath. Dissolve the crude filix acid obtained in this manner in 10 drops of amyl alcohol, using a gentle heat if necessary, then add 10 cubic centimeters of methyl alcohol (added drop by drop at the beginning and later rapidly.) Set the liquid containing the crystals aside in a cool place for 12 hours, then collect the latter on a tared filter, and, after washing with several 5 cubic centimeter portions of methyl alcohol, dry at a temperature between 60° and 70°C and weigh.

*Improved Method of Fromme (1897):* Place 5 grams of the oleoresin, 30 grams of ether and 100 grams of a solution of barium hydroxide (1 per cent.) in a 200 cubic centimeter flask and shake for 5 minutes. Then run the mixture into a separatory funnel, and, after allowing it to stand for 10 to 15 minutes, run off into another separatory funnel 86 grams (corresponding to 4 grams of the oleoresin) of the lower aqueous layer. Acidify by the addition of hydrochloric acid (25 to 30 drops) and shake out with ether (in 25, 15, 10 and 10 cubic centimeter portions.) Filter the combined ether washings into a 100 cubic centimeter flask and evaporate to dryness on a water bath. Dissolve the residue in 1 cubic centimeter of amyl alcohol by heating over a free flame and precipitate the pure filix acid with 30 cubic centimeters of methyl alcohol (added drop by drop until a permanent precipitate is produced, and the remainder at once.) After the liquid has stood quietly in a cool place for 10 to 12 hours, collect the precipitate on a tared filter, wash with methyl alcohol (two 5 cubic centimeter portions,) press the filter between porous plates, dry at an initial temperature of 40°C and finally at 80°C, and weigh.

*Stoder's Method (1901):* Dissolve 5 grams of the oleoresin in 20 cubic centimeters of ether, add 100 cubic centimeters of a freshly prepared solution of barium hydroxide (2 per cent.) and shake the mixture frequently during 1 hour. After allowing the mixture to stand quietly for a short time, separate the lower aqueous layer by filtration. Collect 86 cubic centimeters of this portion (corresponding to 4 grams of the oleoresin) in a separatory funnel and acidify with 10 cubic centimeters of dilute hydrochloric acid. Shake out the resulting precipitate with three portions of ether (40, 30 and 20 cubic centimeters) added successively, unite the shakings and remove the solvent by distillation. Dissolve the



residue in 1 cubic centimeter of amyl alcohol, and, after the solution has stood in a cool place for 48 hours, add 15 cubic centimeters of methyl alcohol. After standing for 24 hours more, collect the precipitated filix acid on a filter, wash with 5 cubic centimeters of methyl alcohol, dry on a water bath and weigh.

It will be noticed that the preceding methods, with the exception of the one devised by Kremel, are very similar in general outline, practically the only difference being found in the procedure by which the crude filix acid is directed to be purified. This difference is of special importance, however, as the weight of the product finally obtained will naturally vary with the degree to which purification has been effected, and this in turn will cause the computed percentage to vary, as is shown in the following table:

TABLE 27.—*Variation in filix acid content due to the difference in the methods employed in its determination.*

Date	Observer	Per cent. of filix acid by the method of			
		Bocchi	Kraft	Fromme (Original)	Fromme (Improved)
1897	Gehe & Co.....	18.24 to 30.25	.....	3.28 to 11.32	.....
1897	Madsen.....	.....	.....	13.07	12.10
1897	.....	.....	.....	6.58	5.85
1898	Plzak.....	.....	6.48	6.00	5.20

The above table shows further that the filix acid is obtained in the state of greatest purity when the improved method of Fromme is employed. And this method was usually given preference in the valuation of the oleoresin until it was discovered that the teniafuge properties were not due to the filix acid, alone, but were to be attributed in part to the presence of a number of other substances as well, compounds resembling acids to a certain extent in their chemical behavior.

#### *Methods for the determination of the Crude Filicin.*

With the above mentioned advance in our knowledge concerning the therapeutic constituents of this preparation, the methods for the determination of the filix acid lost their value and have since been superseded by those which have for their

object the determination of the quantity of total active constituents (crude filicin) present. The methods which have been proposed for this purpose are as follows:

*Method of Rulle (1867):*<sup>1</sup> Add a liberal amount of water to a weighed portion of the oleoresin contained in a suitable flask and heat on a water bath at 40° to 50°C. Add sufficient ammonia water to produce a strong odor of the same after vigorously shaking. Allow the mixture to stand in cold water for 3 or 4 hours and add 1/5 to 1/4 of its volume of a saturated solution of salt, then filter. Wash the flask and filter with the salt solution, diluted with 6 parts water, until the filtrate no longer gives a precipitate with hydrochloric acid. Add dilute hydrochloric acid to the filtrate until precipitation is complete, collect the precipitate on a filter, wash and dry over sulphuric acid until of constant weight.

*Method of Dacomo and Secocianti (1896):*<sup>2</sup> Dissolve 1 to 3 grams of the oleoresin in a small quantity of ether and shake the solution for 1/2 hour with an equal volume of an aqueous copper acetate solution. Allow the mixture to stand and separate, decant the ethereal liquid and collect the precipitate on a tared filter. Wash it successively with water, alcohol and ether, then heat at 100°C until of constant weight. When dry 111.55 parts of the precipitate represent 100 parts of filix acid.

*Method of Schmidt (1903):*<sup>3</sup> Place 5 grams of the oleoresin in a mortar and convert it to a coarse powder by triturating it with a sufficient quantity of calcined magnesia. Then add 250 cubic centimeters of water and thoroughly mix. After the magnesia has settled, decant the aqueous portion on a filter. Repeat this operation twice using 150 cubic centimeters of water each time. Transfer the combined filtrate to a separatory funnel and add hydrochloric acid in sufficient quantity to produce complete precipitation. Shake out the precipitate with ether, specific gravity 0.720 to 0.722, added in successive portions (100, 50 and 30 cubic centimeters.) After filtering the ethereal shakings, remove the solvent by distillation and dry the residue at 100°C.

*Method of Fromme (1905):*<sup>4</sup> Dissolve 5 grams of the extract in 30 grams of ether, add 100 grams of a saturated solution (3 per cent.) of barium hydroxide, and shake the mixture vigorously during several minutes. Transfer to a separator, and run 86 grams (4 grams of the extract) of the lower aqueous layer into a flask of 200 cubic centimeters capacity. Add 2 grams of hydrochloric acid (25 per cent.) and shake out with 3 portions of ether, 25, 15, and 10 cubic centimeters. Separate the ether, and filter each portion successively through the same plain double filter into an

<sup>1</sup> Cited by Doesterbehn (1898).

<sup>2</sup> This procedure was proposed as a method for the estimation of the filix acid. As its nature and the results obtained in its application show that it is in reality a method for determining the total constituents of an acid character, it has been included here.

<sup>3</sup> The method proposed by Goris and Voisin (1913) is almost identical with the above, the only difference being that 2 to 3 grams of the oleoresin are taken instead of 5 grams as directed by Schmidt.

<sup>4</sup> This is the method (but slightly modified) which is official in the British, Finnish and Swiss pharmacopœias.

Erlenmeyer flask of 200 cubic centimeters capacity which has been previously weighed. Wash the filter with 10 cubic centimeters more of ether, and finally distill off the ether and dry the residue at 100°C. Weigh after allowing it to stand in a desiccator for half an hour. The weight multiplied by 25 will give the percentage of crude filicin in the sample.

The striking similarity in the above methods is quite apparent and needs no special mention. Attention, however, is invited to the principal point of difference, namely, the reagent employed for the purpose of rendering the constituents to be determined soluble in water. In the methods under consideration, ammonia water, magnesium oxide and barium hydroxide have been made use of. As the amount of crude filicin obtained has been shown to depend to a considerable extent upon which one of these reagents is employed, the difference in the results reported in the literature in this connection is readily accounted for. The importance of this factor is clearly brought out in the following data obtained by Hill:

TABLE 28—*Influence of different alkalis on the percentage of crude filicin obtained.*

Alkali	$K_2CO_3$	1 per cent KOH	6 per cent. KOH	$Mg(OH)_2$	$Ca(OH)_2$	$Ba(OH)_2$
Per cent. of crude filicin .....	37.6	37.9	33.8	13.6	20.0	21.6

These results would appear to indicate that potassium hydroxide is the most efficient reagent for effecting a soluble combination of the constituents comprising the so-called crude filicin. The data, however, are misleading in that the strong alkali combines with other material therapeutically inert, and thereby causes the results to be high. While there is no information of a physiological nature at hand to substantiate the statement that barium hydroxide is the best reagent for this purpose, it is nevertheless, thought to be the most satisfactory from a chemical stand point at least. The method of Fromme, in which the latter is directed to be used, was, therefore, employed in the evaluation of the oleoresins examined in the laboratory. The results obtained in these analyses, together with those reported by other workers are given in the table which follows:

TABLE 29.—*Crude filicin content of laboratory samples of the oleoresin determined by Fromme's method.*

Sample No.	Date	Observer	Solvent	Crude filicin
				Per cent.
1.....	1898	Bellingrodt.....	Ether.....	18.20
2.....	"	".....	".....	18.96
3.....	"	".....	".....	19.82
4.....	"	".....	".....	20.38
5.....	"	".....	".....	20.87
6.....	"	".....	".....	21.76
7.....	"	".....	".....	21.85
8.....	"	".....	".....	24.32
1.....	1899	Caesar & Loretz.....	".....	31.44 <sup>1</sup>
2.....	"	".....	".....	27.48 <sup>2</sup>
1.....	1913	Bohrisch.....	".....	18.22
1.....	"	DuMez.....	Acetone.....	13.79
2.....	"	".....	Ether.....	20.37
1.....	"	Harrison & Self.....	".....	19.30
2.....	"	".....	".....	19.70
3.....	"	".....	".....	21.50
4.....	"	".....	".....	21.90
5.....	"	".....	".....	24.10
6.....	"	".....	".....	24.20
7.....	"	".....	".....	24.50
8.....	"	".....	".....	24.70
9.....	"	".....	".....	26.50
10.....	"	".....	".....	27.70
11.....	"	".....	".....	28.0
1.....	1914	Linke.....	".....	19.30
2.....	1916	DuMez.....	Acetone.....	16.00 <sup>3</sup>
2.....	"	".....	Ether.....	16.27 <sup>3</sup>

<sup>1</sup> Ether, specific gravity 0.720.<sup>2</sup> Ether, specific gravity 0.723.<sup>3</sup> Oleoresins which were prepared in 1910 and had deteriorated. Examined shortly after being prepared, the ethereal oleoresin showed a crude filicin content of 26.35 per cent.

From the foregoing, it is apparent that the crude filicin content is influenced<sup>1</sup> by the age of the oleoresin as well as by the solvent which has been employed in its preparation. In the case of acetone, the low results obtained are not due to the incomplete extraction of the constituents to be determined, as might be inferred, but rather to the relatively large amount of total extractive matter obtained. It will be noticed that when the oleoresin is fresh and ether is the solvent which has been used in its preparation, the crude filicin content is usually above 20 per cent. This is in accordance with the requirements of the British Pharmacopœia and is thought to be a more reasonable standard than that adopted by the Swiss, or the Finnish pharmacopœias. The former requires a filicin content of 26 to 28 per cent, while the latter specifies a minimum content of 26 per cent. This statement is further supported by the results obtained in the examination of commercial samples as is shown in the following compilation of such data:

<sup>1</sup> For the effect of the condition of the rhizomes used on the crude filicin content, see under "Drug used, its collection, preservation, etc."

Sample No.	Date	Observer	Source	Crude filicin
				Per cent.
1.....	1901	Caesar & Loretz.....	Prepared by the firm.....	21.40
2.....	"	" " " " " " " "	" " " " " " " "	26.15
3.....	"	" " " " " " " "	" " " " " " " "	27.37
4.....	"	" " " " " " " "	" " " " " " " "	28.17
5.....	"	" " " " " " " "	" " " " " " " "	30.00
6.....	"	" " " " " " " "	" " " " " " " "	30.12
7.....	"	" " " " " " " "	" " " " " " " "	30.30
8.....	"	" " " " " " " "	" " " " " " " "	30.92
1.....	1903	" " " " " " " "	" " " " " " " "	27.08
2.....	"	" " " " " " " "	" " " " " " " "	28.22
3.....	"	" " " " " " " "	" " " " " " " "	28.78
4.....	"	" " " " " " " "	" " " " " " " "	29.39
5.....	"	" " " " " " " "	" " " " " " " "	30.05
6.....	"	" " " " " " " "	" " " " " " " "	36.60
1.....	1911	Evans Sons, Lescher & Webb.....	England.....	26.30
2.....	"	" " " " " " " "	" " " " " " " "	28.00
1.....	"	Parry.....	" " " " " " " "	8.40 <sup>(1)</sup>
2.....	"	" " " " " " " "	" " " " " " " "	8.60 <sup>(1)</sup>
3.....	"	" " " " " " " "	" " " " " " " "	8.80 <sup>(1)</sup>
4.....	"	" " " " " " " "	" " " " " " " "	9.00 <sup>(1)</sup>
5.....	"	" " " " " " " "	" " " " " " " "	9.20 <sup>(1)</sup>
6.....	"	" " " " " " " "	" " " " " " " "	10.80 <sup>(1)</sup>
1 to 16..	1912	Evans Sons, Lescher & Webb.....	.....	22.90 to 26.30
1.....	"	Southall Bros. & Barclay.....	" " " " " " " "	6.09 <sup>(1)</sup>
2.....	"	" " " " " " " "	" " " " " " " "	7.16 <sup>(1)</sup>
3.....	"	" " " " " " " "	" " " " " " " "	26.04
4.....	"	" " " " " " " "	" " " " " " " "	28.76
1.....	1913	Bohrisch.....	Germany.....	14.85
2.....	"	" " " " " " " "	" " " " " " " "	15.42
3.....	"	" " " " " " " "	" " " " " " " "	16.00
4.....	"	" " " " " " " "	" " " " " " " "	24.00
1.....	"	DuMez.....	England.....	8.79
2.....	"	" " " " " " " "	United States.....	14.36
3.....	"	" " " " " " " "	Germany.....	16.55
4.....	"	" " " " " " " "	England.....	17.51 <sup>(1)</sup>
5.....	"	" " " " " " " "	Germany.....	20.32
6.....	"	" " " " " " " "	United States.....	20.77
1 to 7	1913	Evans Sons, Lescher & Webb.....	Not given.....	21.3 to 25.30
8.....	"	" " " " " " " "	" " " " " " " "	15.60 <sup>(1)</sup>
9.....	"	" " " " " " " "	" " " " " " " "	19.60 <sup>(1)</sup>
10.....	"	" " " " " " " "	" " " " " " " "	19.70 <sup>(1)</sup>
.....	"	Goris & Volsin.....	Germany.....	13.61 to 19.00
.....	"	" " " " " " " "	Switzerland.....	7.13 to 24.00
.....	"	" " " " " " " "	France.....	20.60 to 22.13
1.....	"	Harrison & Self.....	Germany.....	13.70
2.....	"	" " " " " " " "	" " " " " " " "	19.10
3.....	"	" " " " " " " "	" " " " " " " "	21.20
4.....	"	" " " " " " " "	" " " " " " " "	24.80
5.....	"	" " " " " " " "	" " " " " " " "	25.80
6.....	"	" " " " " " " "	" " " " " " " "	28.10
1.....	"	Hill.....	England.....	11.60 <sup>(1)</sup>
2.....	"	" " " " " " " "	" " " " " " " "	13.20 <sup>(1)</sup>
3.....	"	" " " " " " " "	" " " " " " " "	14.10 <sup>(1)</sup>
4.....	"	" " " " " " " "	Not given.....	18.10
5.....	"	" " " " " " " "	" " " " " " " "	18.92
6.....	"	" " " " " " " "	" " " " " " " "	19.30
7.....	"	" " " " " " " "	" " " " " " " "	20.22
8.....	"	" " " " " " " "	" " " " " " " "	20.67
9.....	"	" " " " " " " "	" " " " " " " "	21.57
10.....	"	" " " " " " " "	" " " " " " " "	21.60
11.....	"	" " " " " " " "	" " " " " " " "	22.00
12.....	"	" " " " " " " "	" " " " " " " "	22.65
13.....	"	" " " " " " " "	" " " " " " " "	23.10

TABLE 30.—Continued.

Sample No.	Date	Observer	Source	Crude filicin
				Per cent.
14.....	1913	Hill.....	Not given.....	23.72
15.....	"	".....	" ".....	23.75
16.....	"	".....	" ".....	24.50
17.....	"	".....	" ".....	24.55
18.....	"	".....	" ".....	25.15
19.....	"	".....	" ".....	25.27
20.....	"	".....	" ".....	27.10
21.....	"	".....	" ".....	27.82
22.....	"	".....	" ".....	28.10
23.....	"	".....	" ".....	29.75
1.....	1914	Linke.....	Merck & Co.....	20.40
2.....	"	".....	Brueckner, Lampe & Co..	21.67
3.....	"	".....	Caesar & Loretz.....	27.22
1.....	1915	Southall Bros. & Barclay	Not given.....	20.40
2.....	"	" " " ".....	" ".....	21.60
3.....	"	" " " ".....	" ".....	24.20
4.....	"	" " " ".....	" ".....	24.60
5.....	"	" " " ".....	" ".....	27.70
1.....	1916	DuMez.....	Stearns & Co.....	7.79 (*)
2.....	"	".....	Lilly & Co.....	17.57
3.....	"	".....	Squibb & Sons.....	19.04
4.....	"	".....	Parke, Davis & Co.....	22.66

\* These samples were adulterated with castor oil.

\* Apparently an oleoresin from some species of fern other than *Dryopteris filix-mas*.

In addition to the information given in table No. 29, table No. 30 reveals the fact that a low filicin content in the commercial oleoresins is frequently due to adulteration with castor oil.

### Physiological Tests.

In view of the difference in toxicity of the various constituents of the oleoresin with respect to the tapeworm, a physiological method for the evaluation of this preparation would appear to be desirable. The method proposed for this purpose by Yagi indicates the possibilities along this line. However, as there is no available information regarding its application, aside from that given by the originator, no statement can be made concerning its practical value. A description of the method for conducting the test follows:

**Method of Yagi (1914):** After thoroughly drying in a desiccator, accurately weigh 1 gram of the oleoresin and dissolve it in 25 cubic centimeters of ether. Bring the therapeutically active constituents into aqueous solution by shaking the ethereal liquid with a saturated solution of magnesium hydroxide, using 50 cubic centimeters of the latter for every

cubic centimeter of the former. Filter and divide the filtrate into several parts. Prepare solutions of different dilution from these parts by adding a measured amount of water to each. Then immerse 5 earthworms in each of these solutions and note the maximum dilution in which all 5 are killed. For computing the relative value of the preparation compare these results with those obtained when using a standard solution prepared by dissolving a weighed amount of filix acid, filmaron or albaspidin in water in the same manner as described above for the oleoresin. In the case of these standard solutions the limit of toxicity is given as follows: filmaron, 3 parts in 1,000,000; filix acid 4 parts in 1,000,000; albaspidin 1 part in 100,000.

### *Adulterations*

The efforts which have been made in recent years to standardize this preparation have resulted in the discovery that the commercial article is very frequently adulterated, the latter being accomplished in a variety of ways.

The method usually resorted to by unscrupulous manufacturers in order to increase their profits consists of diluting the finished product with some comparatively cheap material. Castor oil<sup>1</sup> has generally been used for this purpose. In some cases, the oleoresin is prepared from deteriorated brown rhizomes and made to assume the green color of the official preparation by the addition of chlorophyll or salts of copper.<sup>2</sup>

Adulteration, however, is not limited to the addition of foreign materials to the finished product, but may take place in the drug from which the oleoresin is prepared. The forms in which the drug may be contaminated are conveniently classed under three heads, viz.: (a) the substitution of old deteriorated rhizomes for the fresh material, (b) the admixture of chaff and dead stipe bases with the rhizomes, and (c) the admixture of rhizomes of unofficial species of fern with those of the official species. For a discussion of these conditions, see under "Drug used, its collection, preservation, etc."

<sup>1</sup> Parry (1911); Evans Sons, Lescher and Webb (1911); and others.

<sup>2</sup> Weppen and Lueders (1892); Beckurts and Peters (1893); Pendorff (1913); and others.

A trace of copper is usually present in the commercial product as a result of the use of copper utensils in the manufacture of the preparation. (See under "Ash").

## OLEORESIN OF CAPSICUM

*Synonyms*

- Aetherische Spanishpfefferextrakt*, Nat. Disp. 1884.  
*Capsicum*,<sup>1</sup> Chem. & Drugg. (1913), 82, p. 470.  
*Capsicol*, Vierteljahrschr. f. prakt. Pharm. (1873), 22, p. 507.  
*Ethereal Extract of Capsicum*, Am. Journ. Pharm. (1849), 21, p. 114.  
*Extractum Capsici aethereum*, Hirsch, Univ. P. 1902, No. 1905.  
*Oleoresin of Red Pepper*, Stevens, Pharm. and Disp. (1909), p. 255.  
*Oleoresina Capsici*, U. S. P. 1910.  
*Oléorésine de Capsique*, U. S. Disp. 1907.  
*Spanishpfefferextrakt*, Nat. Disp. 1884.  
*Spanishpfeffer-Oelharz*, Nat. Disp. 1884.

*History*

The oleoresin of capsicum appears to have been first prepared by Procter in 1849, and it was through his efforts that it was introduced into the *United States Pharmacopœia* of 1860. Up to the present time, no such preparation appears in any of the foreign pharmacopœias. A similar preparation known as capsicin has, however, been in use in Europe since 1873.<sup>2</sup>

*Drug Used, Its Collection, Preservation, Etc.*

The drug directed to be used by the present edition of the *United States Pharmacopœia* is "the dried ripe fruits of *Capsicum frutescens* Linné<sup>3</sup> (Fam. *Solanaceae*), without the presence or admixture of more than 2 per cent. of stems, calyxes or other foreign matter." The preceding editions of the Pharmacopœia since 1880 have specified the use of the species known as *Capsicum fastigiatum* Blume. The change is evidently due to the fact that the leading commercial varieties of Cayenne pepper are at the present time being received from Africa and Japan and

<sup>1</sup> For other uses of the term capsicin, see under "Chemistry of capsicum and its oleoresin."

<sup>2</sup> Buchheim states that capsicin (the ethereal extract of capsicum) was being prepared and sold by Merck of Darmstadt in 1873. Vierteljahrschr. f. prakt. Pharm. (1873), 22, p. 507.

Capsicin, as found on the market in England, is stated to be indefinite in that it may be an alcoholic, a chloroformic, an ethereal or an acetone preparation. Chem. and Drugg. (1913), 82, p. 470.

<sup>3</sup> This is also the species recognized by the French Pharmacopœia. In the other European pharmacopœias, in which this drug occurs, it is usually the the larger fruited variety, *Capsicum annum*, which is designated.



belong to the first mentioned species<sup>4</sup> which has also been known as *Capsicum baccatum* Vell.

The fruit is plucked when ripe, exposed to the sun until dried, and then usually packed in suitable shape for market. It should be preserved in the whole condition in a cool place,<sup>5</sup> and preferably in a closed container as it is prone to become rancid owing to the large amount of fatty oil which it contains.

### *U. S. P. Texts and Comments Thereon.*

The oleoresin has been official in the *United States Pharmacopæia* for the past half century having been recognized for the first time in the edition of 1860.

1860

#### Oleoresina Capsici

##### Oleoresin of Capsicum

Take of Capsicum,<sup>1</sup> in fine powder,<sup>2</sup> distillation on a water-bath, eighteen  
twelve troy-ounces; fluid-ounces of ether,<sup>3</sup> and expose the

Ether<sup>3</sup> a sufficient quantity.

Put the capsicum into a cylindrical percolator,<sup>4</sup> press it firmly, and gradually pour ether upon it until twenty-four fluid ounces of filtered liquid have passed.<sup>5</sup> Recover from this, by

residue, in a capsule, until the remaining ether has evaporated.<sup>7</sup> Lastly, remove, by straining, the fatty matter which separates on standing,<sup>8</sup> and keep the Oleoresin in a well-stoppered bottle.<sup>9</sup>

1870

#### Oleoresina Capsici

##### Oleoresin of Capsicum

Take of Capsicum,<sup>1</sup> in fine powder,<sup>2</sup> ounces of liquid have slowly passed.<sup>6</sup>  
twelve troyounces; Recover the greater part of the ether

Ether<sup>3</sup> a sufficient quantity.

Put the capsicum into a cylindrical percolator, provided with a stop-cock, and arranged with cover and receptacle suitable for volatile liquids,<sup>4</sup> press it firmly, and gradually pour ether upon it, until twenty-four fluid

by distillation on a water-bath,<sup>5</sup> and expose the residue in a capsule, until the remaining ether has evaporated.<sup>7</sup> Lastly, remove, by straining, the fatty matter which separates on standing,<sup>8</sup> and keep the Oleoresin in a well-stoppered bottle.<sup>9</sup>

<sup>4</sup> Tolman and Mitchell, Bull. 163, Bur. of Chem. (1913), p. 9.

<sup>5</sup> Brown, Bull. 150, Kentucky Agric. Exp. Sta. (1910), p. 131.

1880

## Oleoresina Capsici

## Oleoresin of Capsicum

Capsicum,<sup>1</sup> in No. 60 powder,<sup>2</sup> *one* residue, in a capsule, until the remain-  
*Hundred parts* ..... 100 ing ether has evaporated.<sup>1</sup> Lastly,  
 Stronger Ether,<sup>3</sup> *a sufficient quantity.* pour off the liquid portion,<sup>2</sup> transfer

Put the capsicum into a cylindrical the remainder to a strainer, and, when  
 percolator, provided with a cover and the separated fatty matter (which is  
 receptacle suitable for volatile liquids,<sup>4</sup> to be rejected) has been completely  
 press it firmly, and gradually pour drained, mix all the liquid portions to-  
 stronger ether upon it, until one hun- gether.<sup>2</sup>

dred and fifty (150) parts of liquid Keep the oleoresin in a well stop-  
 have slowly passed.<sup>5</sup> Recover the ped bottle.<sup>20</sup>  
 greater part of the ether by distilla- Preparation. Emplastrum Capsici.  
 tion on a water-bath,<sup>6</sup> and expose the

1890

## Oleoresina Capsici

## Oleoresin of Capsicum

Capsicum,<sup>1</sup> in No. 60 powder,<sup>2</sup> *five* a water-bath,<sup>6</sup> and, having transferred  
*hundred grammes* ..... 500 Gm. the residue to a capsule, allow the re-  
 Ether,<sup>3</sup> *a sufficient quantity.* maining ether to evaporate spontan-

Put the capsicum into a cylindrical eously.<sup>1</sup> Then pour off the liquid por-  
 glass percolator, provided with a stop- tion, transfer the remainder to a  
 cock, and arranged with cover and strainer, and, when the separated fatty  
 receptacle suitable for volatile liquids,<sup>4</sup> matter (which is to be rejected) has  
 Press the drug firmly, and percolate been completely drained, mix the li-  
 slowly with ether, added in successive quid portions together.<sup>2</sup>

portions, until the drug is exhausted.<sup>5</sup> Keep the oleoresin in a well-stop-  
 Recover the greater part of the ether pered bottle.<sup>20</sup>

from the percolate by distillation on Preparation: Emplastrum Capsici.

1900

## Oleoresina Capsici

## Oleoresin of Capsicum

Capsicum,<sup>1</sup> in No. 40 powder,<sup>2</sup> *five hundred grammes* ..... 500 Gm. *Acetone,<sup>3</sup> a sufficient quantity.*

Introduce the capsicum into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle suitable for volatile liquids.<sup>4</sup> Pack the powder firmly, and percolate slowly with acetone, added in successive portions, until eight hundred cubic centimeters of percolate have been obtained.<sup>5</sup> Recover the greater part of the acetone from the percolate by distillation on a water-bath,<sup>6</sup> and, having transferred the residue to a dish, allow the remaining acetone to evaporate spontaneously in a warm place.<sup>7</sup> Then pour off the liquid portion,<sup>8</sup> transfer the remainder to a glass funnel provided with a pledget of cotton, and when the separated fatty matter (which is to be rejected) has been completely drained, mix the liquid portions together.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

Average dose.—0.030 Gm. = 30 milligrammes ( $\frac{1}{2}$  grain).

1910

## Oleoresina Capsici

## Oleoresin of Capsicum

## Oleores. Capsic.

Capsicum,<sup>1</sup> in No. 40 powder<sup>2</sup> *five hundred grammes* ..... 500 Gm. *Ether,<sup>3</sup> a sufficient quantity.*

Place the capsicum in a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle suitable for volatile liquids.<sup>4</sup> Pack the powder firmly and percolate slowly with ether, added in successive portions, until the percolate measures *eight hundred mls.*<sup>5</sup>

Recover the greater part of the ether from the percolate by distillation on a water-bath,<sup>6</sup> and, having transferred the residue to a dish, allow the remaining ether to evaporate spontaneously in a warm place.<sup>7</sup> Then pour off the liquid portion,<sup>8</sup> transfer the remainder to a glass funnel provided with a pledget of cotton, and, when the separated fatty matter (which is to be rejected) has been completely drained, mix the liquid portions together.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

Preparation — *Eplastrum Capsici.*  
Average Dose.—Metric, 0.03 Gm.—Apothecaries,  $\frac{1}{2}$  grain.

1) For a description of the drug, see pag 1017 under "Drug used, its collection, preservation, etc."

2) The editions of the Pharmacopœia previous to that of 1900 directed that the drug be reduced to a fine powder (No. 60) for percolation. As a No. 40 powder has been found to be equally satisfactory for this purpose, the last two editions of the Pharmacopœia have specified the use of the coarser powder.

3) Ether is the solvent which is directed to be used in the extraction of the drug at the present time. Previous editions of the Pharmacopœia, with the exception of that 1900, also, specified the use of ether for this purpose. The use of acetone as directed by the Pharmacopœia of 1900 was unsatisfactory as the large amount of extractive matter obtained caused the residue which remained upon the evaporation of the solvent to assume a semi-solid gelatinous form, and thus increased the difficulty of separating the liquid portion.

Among the other solvents which have received consideration in this connection, benzin is worthy of mention. The reports of Maisch, Trimble and Beringer, respectively, (see part I, pages 923 and 924) indicate that it is a good solvent for the oleoresinous constituents of capsicum and that the product obtained is equal in quality to that yielded by ether. Experiments conducted in the laboratory confirm these observations. The solvent used in the laboratory, however, was petroleum ether, boiling temp. 45 to 50° C., as the composition of ordinary commercial benzin varies to a considerable extent.

4) The Pharmacopœia of 1860 directed that the extraction of the drug be carried out in an ordinary glass percolator. As a considerable amount of solvent was lost under these conditions, the subsequent editions of the Pharmacopœia have specified that a form of percolator adapted to the use of volatile liquids be employed for this purpose. For a description of such forms, see Part I, under "Apparatus used."

5.) Of interest in connection with the preparation of this oleoresin is the fact that the pharmacopœial directions concerning the amount of percolate to be collected have been changed no less than three times. The first change appeared in the Pharmacopœia of 1880, and was apparently instituted for economic reasons as the amount of percolate directed to

be collected was reduced from approximately 2 cubic centimeters for each gram of drug used (24 fluid ounces for 12 troy ounces of drug) to 1.5 cubic centimeters. In the succeeding edition of the Pharmacopœia (edition of 1890), the second change was made, the directions being to continue percolation until the drug is exhausted. The third change occurs in the Pharmacopœia of 1900, which directs that 1.6 cubic centimeters of percolate be collected for each gram of drug taken.

The reason for making the second change does not become apparent from the information at hand. The third change, however, appears to have been instituted primarily for the purpose of reducing the amount of solid fats (mainly palmitin and stearin) extracted in order that the separation of the liquid portion constituting the oleoresin might be accomplished more easily.

In commenting further upon these changes, it is stated that, in the preparation of the oleoresin in the laboratory, no greater difficulty was experienced in the separation of the liquid portion when the amount of solid fats present was large than when the quantity present was relatively small. From this standpoint, therefore, the last change does not appear to have been warranted. For economic reasons, however, the change was desirable since at least twice as much ether was required for the complete exhaustion of the drug as is ordinarily used when proceeding according to the directions given in the last edition of the Pharmacopœia.

It is thought that the present pharmacopœial method could be still further improved through the use of some form of continuous extraction apparatus for exhausting the drug. Not only would this procedure result in the saving of a large amount of solvent, but the time required to complete the preparation of the oleoresin would be considerably shortened.

6) The Pharmacopœia of 1860 directed that only  $\frac{3}{4}$  of the menstruum contained in the percolate be recovered by distillation on a water bath. In all of the subsequent editions the directions are to recover the greater part of the solvent, no specific amount being mentioned. In this connection, it may be stated that the preparation will not be injured even if all of the solvent is recovered under the above conditions. In case this is done, however, it is necessary to use ether in re-

moving the thick liquid from the flask so that no particular advantage is gained by such a procedure.

7) In all editions of the Pharmacopœia in which this preparation is official, it is directed that the last traces of solvent be allowed to evaporate spontaneously at room temperature. Since the complete removal of the solvent can be accomplished much more rapidly by heating the ethereal liquid on a water bath, and without injury to the finished product, it is thought that such a procedure would be a desirable improvement over the present pharmacopœial method.

8-9) The liquid portion constituting the oleoresin is directed to be separated from the solid fats, which precipitate upon the removal of the solvent, by decantation, and straining through a pledget of cotton. Experience has shown that this may be accomplished much more rapidly and satisfactorily by the aid of a force filter. By this procedure a more complete separation can be effected without washing the residue on the filter with a portion of the solvent as has been suggested by some and thus, the necessity of further exposure of the preparation to the air is done away with.

With further reference to the removal of the solid fats, attention is called to the fact that the degree to which this is accomplished depends upon the temperature at which the operation is carried out. The preparation when made during the summer may be perfectly homogeneous at the time, but deposit fat during the winter. In order to secure a more uniform product, it is therefore, thought that the Pharmacopœia should direct that the mixture be chilled to a definite temperature previous to the separation of the liquid portion.

10) The oleoresin should be kept in well-stoppered bottles for the same reasons as are given in the comments on the oleoresin of aspidium. See page 979.

### *Yield*

The average yield of oleoresin is usually about 15 to 18 per cent. when ether is the solvent employed in exhausting the drug. It is about the same when alcohol, acetone, petroleum ether, carbon disulphide or chloroform are used. In this connection, attention is called to the fact that the total amount of

extract obtained and the oleoresin are not identical, the latter consisting only of the oily, liquid portion of the former. Thus, it will be observed, upon examining the tables which follow, that the total amount of extract obtained with acetone may amount to 25 per cent. of the drug operated upon, whereas, the yield of oleoresin is only about 18 per cent. The factor which appears to influence the yield to the greatest extent is the temperature at which the preparation is completed. This is due to the fact that the oleoresin is saturated with solid fats (principally palmitin) and, that these will be precipitated to a greater or lesser degree depending on the temperature at which the preparation is finally strained. The finished product will, therefore, contain a relatively small amount of these fats, and the yield will be correspondingly low when made during the cold winter months, whereas, the opposite will be the case when the oleoresin is prepared in the hot months of summer. The following tables show the yield of oleoresin, as reported in the literature, likewise, that obtained in the laboratory:

TABLE 31.—Yield of oleoresin as reported in the literature.

Date	Observer	Yield of oleoresin to				Remarks
		Alco- hol	Acce- tone	Ether	Other solvents	
1853	Bakes.....	Per ct. 25.00	Per ct.	Per ct.	Percent.	
1888	Trimble.....			19.50	Benzin	Yield of oleoresin when prepared by the U. S. P. method. Total yield of extract on complete exhaustion of the drug.
1892	Beringer.....		18.00	17.32		
		28.00	25.00		25.00	
1892	Sherrard.....			15.50 17.40 18.30 18.40 19.00		
1896	Alpers.....					Oleoresin from which deposited fat had been removed.
1898	Winton, Ogden & Mitchell.....			15.81		Total ether extract from "Chilli Colorado."
				16.85		Total ether extract from Natal capsicum.
				21.31		Total ether extract from Nepal capsicum.
				16.19		Total ether extract from Zanzibar capsicum.
1903	Southall Bros. & Barclay.....			15.67		Capsicum minimum total yield to ether, sp. gr. 0.717.
				15.34		Capsicum annum total yield to ether, sp. gr. 0.717.
1905	Vanderkleed....				Solvent(?) 9.40 to 23.90	Reported as yield of oleoresin. The average yield of 8 samples is given as 18.18 per cent.
1905	Gerrard.....	Alcohol (99%) 26.40		18.20	Benzin 18.60 Petrol Ether 16.40 Carbon disulphide 16.70 Chloroform 17.50	Represents yield of total extractive matter.
1907	Patch.....	16.20 to 26.50				Total alcoholic extract. Results obtained in the examination of 10 samples of capsicum.
1908	".....	15.0 to 25.20				Total alcoholic extract.
1908	Vanderkleed....				Solvent(?) 11.59 to 18.85	Reported as yield of oleoresin: Represents the yield from 3 samples of capsicum.
1909	".....				14.34 to 17.95	Reported as yield of oleoresin. Results obtained in the extraction of 5 samples of capsicum.
1910	Southall Bros. & Barclay.....				Benzene 14.00 to 15.40	Total benzene extract.
1910	Eldred.....			11.00 to 26.00		Reported as yield of ether soluble oleoresin. The average yield obtained from 48 samples of capsicum is given as 18.00 per cent.
1910	Vanderkleed.....				Solvent(?) 15.10 to 22.27	Reported as yield of oleoresin. Results obtained in extracting 7 samples of capsicum



TABLE 31.—Yield of oleoresin as reported in the literature—Continued.

Date	Observer	Yield of oleoresin to				Remarks
		Alco- hol	Ace- tone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per cent. Solvent(?)	
1911	Vanderkleed— Continued.	.....	.....	.....	{ 14.70 17.93	Reported as yield of oleo- resin.
1912	Johnson and Johnson.....	.....	.....	16.00 to 19.00	.....	
1912	Vanderkleed.....	.....	.....	.....	{ Solvent(?) 14.41 to 16.70	Reported as yield of ether ex- tract.
1913	Patch.....	19.00 to 24.00	.....	.....	.....	
1913	Vanderkleed.....	.....	.....	.....	{ Solvent(?) 13.10 to 13.10	Reported as yield of oleoresin. Total alcoholic extract. Re- sults obtained in extracting 4 samples of capsicum.
1913	Englehardt.....	.....	.....	.....	{ Solvent(?) 11.00 11.30 13.10 14.80 15.26 15.80	
1914	Rippetoe.....	17.02 to 24.46	.....	16.49 to 17.88	.....	Reported as yield of oleoresin.
1914	Riedel.....	31.90 to 35.30	.....	.....	.....	
1914	Vanderkleed.....	.....	.....	.....	{ Solvent(?) 13.00 to 13.00	Total yield of extract.
1915	Vanderkleed.....	.....	.....	.....	{ Solvent(?) 13.85 to 20.84	

TABLE 32.—Yield of oleoresin obtained in the laboratory.

Date	Observer	Yield of oleoresin to—				Remarks
		Alco- hol	Ace- tone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per cent.	
1910..	DuMez & Netzel.	25.12	20.25	18.33	{ Benzine 16.50.....	Represent e xtract.
1916..	Du Mez .....	29.90 16.40	22.48 17.50	19.98 16.14	{ Petrol. Ether. 18.82..... 16.18.....	

Represents oleoresin separated  
from deposited fat and other  
extractive matter.

*Chemistry of the Drug and Oleoresin.**Tabulation of Constituents.*

The reported analyses<sup>1</sup> of the various varieties of red peppers show the constituents of pharmaceutical interest to be as follows: fixed oil, volatile oil, fatty acids, capsaicin, capscine, resin, mucilage, starch, coloring matter and inorganic substances. Most of these substances have been identified in the oleoresin prepared by extracting the fruits with ether. They are the following:

Fatty Oil	Capsaicin	Coloring Matter
Fatty Acids	Capsicine	Ash
Volatile Oil	Resin	

*Occurrence and Description of Individual Constituents.*

**Fatty Oil.** Work on the oil of capsicum has practically been limited to that obtained from the variety official in most of the continental pharmacopœias, namely: *Capsicum annum* L. The properties of the oil of *Capsicum fastigiatum* Bl. as observed by Goetz appears to indicate that it is very likely identical with the former.<sup>2</sup> The oil as obtained from the seeds of *Capsicum annum* Bl.<sup>3</sup> is a yellowish brown, mobile liquid, specific gravity 15.5°C 0.91095; iodine value (Huebls) 119.5; saponification value (Koettsdorffer) 187.2. It is composed of the glyceryl esters of oleic, palmitic and stearic acids.

The oil of capsicum is located in the seeds and is variously stated to comprise from 20<sup>4</sup> to 24.06<sup>5</sup> per cent. of these organs in *Capsicum annum*. The yield as computed by Goetz for the entire fruit of *Capsicum fastigiatum* is 8.4 per cent.. The yield in the case of *Capsicum frutescens* does not appear to have been determined.

<sup>1</sup> Taylor, Am. Journ. Pharm. (1857), 29, p. 303; Buchheim, Vierteljahrschr. f. prakt. Pharm. (1872), 4, p. 507; Proc. A. Ph. A. (1873), 22, p. 106; Strohmmer, Chem. Centralb. (1884), 55, p. 557; Pabst, Arch. d. Pharm. (1892), 230, p. 108; Tolman and Mitchell, Bull. No. 163, Bur. of Chem., Dep. of Agr. (1913), p. 9.

<sup>2</sup> Goetz obtained 15.7 per cent of a yellowish-brown fixed oil from the seeds of *Capsicum fastigiatum* Bl., specific gravity at 25°, 0.919. Goetz, unpublished results.

<sup>3</sup> Buchheim, l. c.; Pabst, l. c.; von Bitto, Landwirt. Versuchs-Stat. (1896), 46, p. 310; Meyer-Essen, Chemiker Ztg. (1903), 27, p. 958.

<sup>4</sup> Meyer-Essen, l. c.

<sup>5</sup> von Bitto, l. c.

**Fatty Acids.**<sup>6</sup> The free fatty acids present have been identified as oleic, palmitic and stearic, palmitic acid predominating in the fruits of *Capsicum annum*. The proportions of these acids as they occur in the fruit of *Capsicum fastigiatum* or *C. frutescens* have apparently not been determined to date.

**Volatile Oil.** The presence of a volatile oil was first noted in the fruits of *Capsicum annum* by Taylor.<sup>7</sup> Pabst isolated a small amount of a volatile liquid having the odor of parsley from the same. Inasmuch as the oleoresin, when prepared from *Capsicum frutescens* has a distinct odor, it is quite probable that a similar volatile oil is also present in the fruit of this variety.

**Capsaicin**<sup>9</sup> Capsaicin is the sharp tasting constituent of the fruits of the various varieties of red pepper. It crystallizes from petroleum ether in colorless plates melting at 60.5°C (Morbitz), 63 to 63.5°C (Micko), 64.5°C (Nelson).<sup>10</sup> The substance is stated to be soluble in water (1:30,000), petroleum ether (1:3,633), ether, alcohol, carbon disulphide and chloroform. According to Morbitz, its composition is represented by the formula  $C_{35}H_{54}N_3O_4$ . Micko<sup>11</sup> does not agree with the latter and has proposed the formula  $CH_3O.C_{17}H_{24}NO.OH$ , as also representing the structure in part.

Capsaicin is stated by Morbitz to be present in the fruit of *Capsicum fastigiatum* to the extent of 0.05 to 0.07 per cent.

<sup>6</sup> Buchheim, Pabst, von Blitto, l. c.

<sup>7</sup> l. c.

<sup>9</sup> The term *capsicin* was first used to designate the sharp tasting principle in red peppers. Bucholz, Taschenb. f. Scheidkuenst. u. Apoth. (1816), 37, p. 1; Landerer, Vierteljahresschr. f. prakt. Pharm. (1854), 2, p. 34. The name was also applied to the ethereal extract of capsicum as marketed by Merck and Co. See note by Buchheim, Vierteljahrschr. f. prakt. Pharm. (1873), 22, p. 507. Later it was used to indicate a coniline-like alkaloid isolated from the fruit of *Capsicum fastigiatum* by Thresh. Pharm. Journ. (1876), 35, p. 941.

In 1873, Buchheim gave the name *Capsicol* to a dark red oily liquid (our present oleoresin) which he considered to be the pungent principle.

*Capsaicin* is the term which was introduced by Thresh to denote the sharp tasting substance isolated by him from the fruits of *Capsicum fastigiatum*. Pharm. Journ. (1876), 36, p. 21. It is the name now generally employed to indicate this substance, although, Morbitz (l. c.) subsequently proposed the name *Capsicutin*.

A more recent investigator, Gabriel de la Puerta, has given the name "capsic acid" to the irritant principle isolated from pimenta. Ann. de la Soc. Espanola de fis. y. quim. (1905), No. 23; Am. Drugg. & Pharm. Rec. (1906), 48, p. 40.

<sup>10</sup> Chem. News (1911), 103, p. 111.

<sup>11</sup> Chem. Centralbl. (1899), 70, p. 293.

The amount present in *Capsicum frutescens* has not been reported.

**Capsicine.** According to Felletar<sup>12</sup> and Thresh,<sup>13</sup> capsicine is present in the fruits of *Capsicum annum* and *C. fastigiatum*. The latter describes it as an alkaloid possessing an odor similar to that of coniine. The hydrochloride is stated to have been isolated in the crystalline form and to be precipitated from aqueous solution by the usual alkaloidal reagents. Pabst<sup>14</sup> states that the base is not a normal constituent of the fruits of *Capsicum annum*, but that it is formed when the latter are stored or by the action of various reagents.

**Resin.** Resin is mentioned by several investigators<sup>15</sup> as a constituent of the fruits of the red peppers. Apparently nothing has been done toward determining its composition or properties.

**Coloring Matter.** The red color of the capsicum fruit as well as that of the ethereal extract appears to have attracted the attention of all investigators, although, Pabst, is the only observer who attempted to identify the substance. He concluded, from saponification experiments, that it was a cholesterin ester of a fatty acid.<sup>16</sup>

**Ash.** According to von Bitto,<sup>17</sup> the ash of capsicum is composed of the basic elements, K, Na, Mg, Ca, Fe, Al and Mn combined with the acid radicles Cl', SiO<sub>3</sub>", SO<sub>4</sub>", PO<sub>4</sub>", NO<sub>3</sub>' and CO<sub>3</sub>".

The ash content of red pepper varies with the variety of the fruit.<sup>18</sup> That of the commercial drug is also influenced by the presence of sand. The ash of *Capsicum frutescens* (sand free) amounts to about 4.90 per cent of the dried fruit.<sup>19</sup>

<sup>12</sup> Vierteljahrscr. f. prakt. Pharm. (1868), 17, p. 360; Buchner's Repert. f. d. Pharm. (1828), 27, p. 35; Proc. A. Ph. A., (1871), 19, p. 289.

<sup>13</sup> Pharm. Journ. (1876), 35, p. 941.

<sup>14</sup> l. c.

<sup>15</sup> Strohmer, Pabst, Tolman and Mitchell, l. c.

<sup>16</sup> Pabst, l. c.

<sup>17</sup> Landw. Versuchsstat. (1893), 42, p. 369.

<sup>18</sup> Tolman and Mitchell give the ash content of sand free *Capsicum annum* as 6.69 to 7.54 per cent. Bull. 163, Bur. of Chem., Dept of Agr., Washington, 1913.

<sup>19</sup> McKeown gives the ash content of *Capsicum fastigiatum* as 4.50 to 4.95 per cent. Am. Drugg. (1886), 14, p. 128.

Tolman and Mitchell report the sand free ash content of *Capsicum frutescens* (African) as 4.49 to 5.44 per cent, that of the fruits of the same variety coming from Japan as 4.60 to 5.35 per cent, l. c.

*Constituents of Therapeutic Importance*

The early investigators assigned the intensely irritating properties of the oleoresin of capsicum to various substances supposed to be contained therein. Bracconot<sup>1</sup> and Buchheim<sup>2</sup> thought it due to the oily constituents, Felletar<sup>3</sup> attributed the action to a liquid organic base, and Pabst<sup>4</sup> to a resin intimately mixed with the red pigment. The irritating principle is now known to be the crystalline constituent, capsaicin.<sup>5</sup> The latter has not been isolated in sufficient quantities to permit of an extensive investigation of its physiological properties. It is, however, known to act as a rubefacient when applied externally, and to be extremely pungent to the taste, its sharpness being perceptible in aqueous solution, 1 part to 11 million parts of water.<sup>6</sup>

*Physical Properties*

**Color:** The color of the oleoresin, when the latter is spread out in a thin layer on a white porcelain surface, is a characteristic light brownish-red. The descriptions of the color given in pharmaceutical literature vary to a considerable extent (light reddish-brown to dark brown) owing very likely to a difference in the conditions under which the observations were made.

**Odor:** The odor of the preparation is rather faint, but characteristic, resembling that of the red peppers.

**Taste:** It is extremely pungent and should be tasted with caution. The taste is usually described as being hot and fiery, or burning.

**Consistence:** The consistence of the oleoresin varies with the amount of solid fats (palmitin and stearin) present,<sup>7</sup> and with

<sup>1</sup> Ann. Chim. Phys. (1817), 6, p. 122.

<sup>2</sup> Vierteljahresschr. f. prakt. Pharm. (1873), 22, p. 507.

<sup>3</sup> *Ibid.* (1868), 17, p. 360.

<sup>4</sup> Arch. d. Pharm. (1892), 230, p. 108.

<sup>5</sup> Micko, Zeitschr. f. Unters. Nahr.-u. Genussm. (1898), 12, p. 215.

<sup>6</sup> Morbitz, Pharm. Zeitschr. f. Russland, (1897), p. 372.

<sup>7</sup> See under "Methods of preparation".

the temperature. At ordinary temperatures the degree of fluidity is usually such that it can be readily poured. It should be homogeneous and not contain a deposit of fat.

**Solubility:** The oleoresin, when prepared with ether, is soluble in acetone, ether, chloroform, carbon tetrachloride, carbon disulphide, petroleum ether, oil of turpentine<sup>1</sup> and solutions of the caustic alkalies. It should not be soluble to any great extent in 90 per cent. alcohol, solubility therein indicating that alcohol was the menstruum used in the preparation of the oleoresin.

**Specific gravity:** The specific gravity of the oleoresin determined at 25°C was found to be 0.925 to 0.932 when ether was the solvent employed in extracting the drug. When alcohol or acetone were employed for this purpose, the results were almost the same, whereas petroleum ether yielded a product of low specific gravity. The low specific gravity observed in the one case, where acetone was used in the preparation of the oleoresin, was not due to the nature of the solvent, but to the more complete removal of the solid fats. The variation in the amounts of the latter retained in the finished product is thought to be the chief factor influencing the specific gravity of this preparation. In the case of the commercial samples, however, the presence of unevaporated solvent must also be taken into consideration as is shown in the tables which follow:

TABLE 33—*Specific gravities of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Specific gravity
				At 25° C
1.....	1910	DuMez & Netzel.....	Alcohol.....	0.932
2.....	"	" ".....	Acetone.....	0.933
3.....	"	" ".....	Ether.....	0.932
4.....	"	" ".....	Benzine.....	0.925
1.....	1916	DuMez.....	Alcohol.....	0.926
2.....	"	".....	Acetone.....	0.919
3.....	"	".....	Ether.....	0.925
4.....	"	".....	Petrol. ether.....	0.914

<sup>1</sup> King's American Dispensatory (1900), p. 1331.

TABLE 34—*Specific gravities of commercial oleoresins.*

Sample No.	Date	Observer	Source	Specific gravity
1.....	1916	DuMez.....	Squibb & Sons.....	At 25° C
2.....	"	".....	Lilly & Co. ....	0.910 <sup>1</sup>
3.....	"	".....	Sharp & Dohme.....	0.919
				0.928

<sup>1</sup> taine d ether

**Refractive index:** Determinations made in the laboratory show that the oleoresin should have a refractive index of about 1.47 when observed at 25°C. A refractive index lower than this was found to be due to the presence of unevaporated solvent. The solvent employed in extracting the drug or the variation in solid fat content appears to have very little influence, if any, on this constant. The results obtained in the laboratory in the examination of the oleoresin follow:

TABLE 35—*Refractive indices of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Refractive index
1.....	1910	DuMez & Netzel.....	Alcohol.....	At 25° C
2.....	"	".....	Acetone.....	1.468
3.....	"	".....	Ether.....	1.477
4.....	"	".....	Petrol, ether.....	1.474
1.....	1916	DuMez.....	Petrol, ether.....	1.475
2.....	"	".....	Alcohol.....	1.478
3.....	"	".....	Acetone.....	1.478
4.....	"	".....	Ether.....	1.474
			Petrol, ether.....	1.472

TABLE 36.—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
1.....	1916	DuMez.....	Lilly & Co.....	At 25° C
2.....	"	".....	Sharp & Dohme.....	1.472
3.....	"	".....	Squibb & Sons.....	1.478
				1.467 <sup>1</sup>

<sup>1</sup> Contained ether.

*Chemical Properties.*

*Loss in weight on heating:* Determinations made in the laboratory show that the oleoresin loses but little in weight on heating at 110°C, a loss of but 0.42 to 2.13 per cent. having been observed for the preparation when free from solvent. The laboratory preparations as a rule showed a smaller loss than the commercial samples, which is very likely due to a difference in the temperature conditions under which the preparations were made. The results obtained in the determinations made in the laboratory are given in the following tables:

TABLE 37—*Laboratory preparations—loss in weight on heating*

Sample No.	Date	Observer	Solvent	Per cent. of loss on heating
				At 110° C
1.....	1916	DuMez .....	Alcohol .....	0.42
2.....	"	" .....	Acetone .....	0.52
3.....	"	" .....	Ether .....	0.88
4.....	"	" .....	Petrol. ether .....	0.68
5.....	"	" .....	Alcohol .....	5.15 <sup>1</sup>
6.....	"	" .....	Acetone .....	0.74
7.....	"	" .....	Ether .....	2.09
8.....	"	" .....	Benzine.....	1.01

<sup>1</sup> Contained alcohol.TABLE 38.—*Commercial oleoresins—loss in weight on heating.*

Sample No.	Date	Observer	Source	Per cent of loss on heating
				At 110° C
1.....	1916	DuMez .....	Sharp & Dohme.....	1.93
2.....	"	" .....	Lilly & Co.....	2.13
3.....	"	" .....	Squibb & Sons.....	4.09 <sup>1</sup>

<sup>1</sup> Contained ether.

*Ash Content:* The determinations made in the laboratory show that the ash content of the oleoresin varies with the solvent employed in its preparation. When acetone was the solvent used, the amount of ash obtained did not exceed 0.26 per cent, whereas, the amount was only 0.09 to 0.12 per cent. when the oleoresin was prepared with ether. The variable results obtained in the examination of the commercial samples appear to



indicate the use of different solvents in their preparation. The comparatively high value (0.40 per cent.) obtained in one case, however, may have been due to the copper present. The ash content of the samples examined in the laboratory is given in the tables which follow:

TABLE 39.—*Ash contents of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Per cent. of ash
1.....	1916	DuMez.....	Alcohol.....	0.39
2.....	"	".....	Acetone.....	0.26
3.....	"	".....	Ether.....	0.09
4.....	"	".....	Petrol, ether.....	0.00
5.....	"	".....	Alcohol.....	0.39
6.....	"	".....	Acetone.....	0.24
7.....	"	".....	Ether.....	0.12
8.....	"	".....	Benzin.....	0.10

TABLE 40.—*Ash contents of commercial oleoresins*

Sample No.	Date	Observer	Source	Per cent. of ash	Foreign constituents
1.....	1916	DuMez.....	Squibb & Sons.....	0.09 <sup>1</sup>	Copper
2.....	"	".....	Sharp & Dohme.....	0.40	
3.....	"	".....	Lilly & Co.....	0.30	

<sup>1</sup> Contained ether.

*Acid number:* The acid numbers, when acetone, ether, or petroleum ether were used in the preparation of the oleoresin, were found to be 106.6, 103.8 and 105 respectively. When alcohol was employed for this purpose, the value obtained for this constant was considerably lower, being 93.5. With respect to the commercial samples examined, the acid number was in all cases found to be much lower. This is thought to be due, in two instances, to a low free acid content (principally palmitic acid) of the drug from which the oleoresins were prepared, or to the more complete removal of these acids in the separation of the deposited material. In the third case, it was caused, in part, at least, by the presence of unevaporated solvent. The acid numbers obtained for the preparations examined in the laboratory are as follows:

TABLE 41—*Acid numbers of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Acid number
1 .....	1916	DuMez .....	Alcohol.....	93.5
2 .....	"	" .....	Acetone .....	106.6
3 .....	"	" .....	Ether .....	103.8
4 .....	"	" .....	Petrol. Ether.....	105.0

TABLE 42—*Acid numbers of commercial oleoresins.*

Sample No.	Date	Observer	Source	Acid number
1 .....	1916	DuMez .....	Squibb & Sons .....	30.8 <sup>1</sup>
2 .....	"	" .....	Sharp & Dohme .....	60.3
3 .....	"	" .....	Lilly & Co. ....	32.7

<sup>1</sup> Contained ether.

*Saponification value:* The saponification values obtained for the oleoresins prepared in the laboratory were above 200, as a rule, regardless of the nature of the solvent used in extracting the drug. The comparatively slight variations observed were very likely due to the difference in the degree to which the solid fats (principally palmitin) had been removed. This also accounts for the comparatively low values obtained for the commercial preparations. The exceptionally low value obtained for the sample from Squibb and Sons is to be attributed to the presence of unevaporated solvent. The values obtained for the preparations examined in the laboratory are given in the tables which follow:

TABLE 43—*Saponification values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Saponification value
1 .....	1916	DuMez.....	Alcohol.....	203.5
2 .....	"	" .....	Acetone .....	209.2
3 .....	"	" .....	Ether .....	207.4
4 .....	"	" .....	Petrol. ether .....	208.6
5 .....	"	" .....	Alcohol.....	196.7
6 .....	"	" .....	Acetone .....	202.8
7 .....	"	" .....	Ether .....	206.9
8 .....	"	" .....	Benzin .....	198.7

TABLE 44—*Saponification values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Saponification value
1.....	1916	DuMez.....	Squibb & Sons.....	193.4 <sup>1</sup>
2.....	"	".....	Sharp & Dohme.....	196.9
3.....	"	".....	Lilly & Co.....	198.3

<sup>1</sup> Contained ether.

*Iodine value:* An iodine value of 122 to 123.9 was obtained for the oleoresins prepared in the laboratory using ether as the extracting menstruum. Results very near the same were obtained when acetone or petroleum ether were the solvents used, whereas, the preparation when made with alcohol gave a lower value, 109.3 to 105.7. The principal cause<sup>1</sup> for the variation in this constant (aside from the effect which the quality of the drug or the solvent may have thereon) as observed in the case of some of the laboratory preparations, as well as the commercial samples, is thought to be the difference in the degree to which the saturated fats (principally palmitin) have been removed. In the case of one of the commercial samples, however, the low iodine value is to be attributed to the presence of unevaporated solvent. The results obtained in the determinations made in the laboratory together with those reported by Kebler for the total ether extract are given in the tables which follow:

TABLE 45.—*Iodine values of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Iodine value
1.....	1913	Kebler <sup>a</sup> .....	Ether.....	107.
2.....	"	".....	".....	123.4
3.....	"	".....	".....	125.2
4.....	"	".....	".....	127.3
5.....	"	".....	".....	132.0
6.....	"	".....	".....	137.3
7.....	"	".....	".....	138.0
8-24.....	"	".....	".....	110.0 to 145.7
1.....	1916	DuMez.....	Alcohol.....	115.7
2.....	"	".....	Acetone.....	125.2
3.....	"	".....	Ether.....	122.0
4.....	"	".....	Petrol. Ether.....	123.7
1.....	"	".....	Alcohol.....	109.3
2.....	"	".....	Acetone.....	118.0
3.....	"	".....	Ether.....	102.9
4.....	"	".....	Benzin.....	116.9

(a) Kebler's results represent the iodine value of the total ether extract.

<sup>1</sup> Lowenstein and Dunn have shown that heating at 110° C. to remove volatile matter from the total ether extract causes a lowering in the iodine value due to absorption of oxygen by the unsaturated fats. *Journ. Indust. and Eng. Chem.* (1910). 2, p. 48.

TABLE 46.—*Iodine values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Iodine value
1.....	1916	DuMez .....	Squibb & Sons .....	109.2 <sup>(1)</sup>
2.....	"	" .....	Sharp & Dohme .....	116.2
3.....	"	" .....	Lilly & Co. ....	121.7

<sup>1</sup> Contained ether.*Special Quantitative Tests.**Physiological Test.*

As the active constituent is present in the oleoresin in such minute quantities that a gravimetric method for its estimation is not practical at the present time, a physiological method would appear to be the best means to employ in the standardization of this preparation. Such a method is reported to be in use for this purpose by the H. K. Mulford Company. Aside, however, from the fact that the test is based on the ability to detect the pungency of the oleoresin in extremely dilute solutions, and that the firm takes as its standard a preparation which is still pungent to the taste in a maximum dilution of 1 to 150,000, there is no exact information available to show in what manner the same is actually carried out. It is thought, however, that a procedure similar to that developed in this laboratory some years ago (1910) is made use of. The following is a description of this method.

Accurately weigh about 1 drop of the oleoresin contained in a small flask, add 5 cubic centimeters of normal potassium hydroxide solution and heat on a water bath for a short time to saponify the fats. Transfer the saponified material to a 100 cubic centimeter flask, using several portions of water for this purpose, and finally dilute up to the mark with more water. With the aid of a pipette, measure off 5 cubic centimeters of this solution and run it into a graduated cylinder (glass stoppered) of 1,000 cubic centimeters capacity. Dilute this with water added in portions of 100 cubic centimeters, tasting the solution after each addition. Note the highest dilution in which the pungent taste is still distinctly perceptible and compare this with the results obtained using a standard preparation.

As all of the samples prepared in this laboratory were found to be distinctly pungent to the taste in dilutions of 1 to 250,000,

it is thought that the standard employed by the H. K. Mulford Company is rather low. In view of these observations, it would appear that a standard of 1 in 200,000 would be more desirable.

### Adulterations

A trace of copper was found in most of the commercial samples examined. See under "Ash content."

## OLEORESIN OF CUBEBA

### Synonyms

- Aetherisches Cubebenextrakt*, Bern. P. 1852.
- Aether-szeszes kúbeba kivonat*, Hung. P. 1888.
- Cubeben Extrakt*, Nethl. P. 1902.
- Estratto di Cubebe*, Swiss P. 1907.
- Estratto di Pepe Cubebe*, Swiss P. 1865.
- Estratto di Pepe Cubebe Etereo*, Ital. P. 1902.
- Ethereal Extract of Cubebe*, Am. Journ. Pharm. (1846), 18, p. 167.
- Extract van Staartpeper*, Nethl. P. 1871.
- Extractu de Cubebe*, Roum. P. 1874.
- Extractum Cubebae Fluidum*, U. S. P. 1850.
- Extractum Cubebarum*, Aust. P. 1906.
- Extractum Cubebarum aethereum*, Swiss P. 1865.
- Extractum Cubebarum aethereo-spirituosum*, Hung. P. 1888.
- Extractum Cubebarum oleoso-resinosum*, Strump, Allg. P. 1861.
- Extractum Kúbebae oleo-resinosum*, Pruss. P. 1829.
- Extrait de Cubebe*, Fr. P. 1884.
- Extrait éthéré de Cubebe*, Bern. P. 1852.
- Extrait oléo-sésineux Cubebe*, Fr. P. 1884.
- Fluid Extract of Cubebs*, U. S. P. 1850.
- Kubebe Extract*, Dan. P. 1869.
- Kubebenextrakt*, G. P. 1872.
- Kubebereextrakt*, Dan. 1893.
- Kubeba Kivonat*, Hung. P. 1875.
- Oelig-Harziges Kubebenextrakt*, Strump, Allg. P. 1861.
- Oleo-Resin of Cubebs*, B. P. 1885.
- Oleo-Resina Cubebae*, B. P. 1885.
- Oleoresina Cubebae*, U. S. P. 1910.
- Oléorésine de Cubebe*, U. S. Disp. 1907.
- Oleoresinous Extract of Cubebe*, Pareira, Mat. Med. 1854.

### History

The oleoresin of cubebe, prepared by extracting the drug with ether and then removing the latter by distillation, was first

brought to the attention of the European pharmacist by Hausmann in 1838. Ten years previous (1828), however, Dublanc in France and simultaneously Oberdoerffer in Germany had made known a similar preparation obtained by a rather long and tedious process involving the distillation of the drug with steam and subsequent extraction of the marc with alcohol. The latter became official in the Prussian Pharmacopœia of 1829 and in the Pharmacopœia of Schleswig-Holstein in 1846, while the former first received official recognition in the Baden Pharmacopœia of 1841.

Through the efforts of Procter, a preparation similar to that made by Hausmann was introduced into the *United States Pharmacopœia* of 1850 under the title *Extractum Cubebae Fluidum*. In the edition of 1860, this title was changed to *Oleoresina Cubebae*. The preparation official in the United States at present is the oleoresin obtained by extracting the cubeb with alcohol, whereas, that which is given recognition in the late European pharmacopœias is the product obtained by exhausting the drug with a mixture of alcohol and ether.

The pharmacopœias of the countries, states and municipalities in which this preparation has been officially recognized, together with the dates of appearance of the various editions in which it received such recognition, are enumerated below.

Prussian Pharmacopœia — 1829, 1833, 1868.

Pharmacopœia of Baden — 1841.

Pharmacopœia of Schleswig-Holstein — 1844.

Pharmacopœia of Berne — 1852.

Belgian<sup>1</sup> Pharmacopœia — 1854, 1855.

United States Pharmacopœia — 1850, 1860, 1870, 1880, 1890, 1900, 1910.

Pharmacopœia of Hannover — 1861.

Pharmacopœia of Hessen — 1862.

Swiss Pharmacopœia — 1865, 1872, 1893, 1907.

Austrian Pharmacopœia — 1869, 1889, 1906.

Danish<sup>1</sup> Pharmacopœia — 1869, 1893.

Hungarian Pharmacopœia — 1871, 1888, 1909.

Netherlands Pharmacopœia — 1871, 1902.

German Pharmacopœia — 1873, 1882, 1890, 1900, 1910.

Roumanian Pharmacopœia — 1874.

French Pharmacopœia — 1884, 1908.

British<sup>1</sup> Pharmacopœia — 1885.

Italian Pharmacopœia — 1902, 1909.

Japanese Pharmacopœia — 1907.

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<sup>1</sup>Not official in the recent editions.

*Drug Used, Its Collection, Preservation, Etc.*

The drug recognized by the ninth revised edition of the *United States Pharmacopœia* is "the dried, unripe fruits of *Piper Cubeba* Linné filius (Fam. *Piperaceae*), without the presence or admixture of more than 5 per cent of stems or other foreign matter." Other botanical synonyms for the same frequently met with in the literature are: *Cubeba Cubeba* (Linné filius) Lyons; and *Cubeba officinalis* Mique.

The fruit is supposedly gathered when full grown, but before ripe, and is immediately packed for exportation. That some of the fruit for sale on the American market is not collected until after ripening would appear to be the case from the color of some of the oleoresins prepared by the author, a condition which has also been noted by the others.<sup>1</sup> In addition, it should also be noted that the so-called *false cubebs*<sup>2</sup> are sometimes substituted for the official drug.

As cubeb gradually deteriorates with age,<sup>3</sup> and in the powdered condition becomes rapidly weaker owing to the loss of volatile oil, it should be stored whole, in closed containers, and powdered only as it is used.

*U. S. P. Text and Comments Thereon.*

The oleoresin has been official in the last seven editions of the *Pharmacopœia*, having been recognized for the first time in the edition of 1850 under the title *Extractum Cubebae Fluidum*.

1850

*Extractum Cubebae Fluidum**Fluid Extract of Cubebs*

Take of Cubebs,<sup>1</sup> in powder,<sup>2</sup> a pound; then distill off, by means of a water-Ether<sup>3</sup> a sufficient quantity. bath, at a gentle heat, a pint and a

Put the Cubebs into a percolator,<sup>4</sup> half of the ether,<sup>5</sup> and expose the and, having packed it carefully, pour residue, in a shallow vessel, until the Ether gradually upon it until two whole of the ether has evaporated.<sup>7</sup> pints of filtered liquor are obtained;<sup>8</sup>

<sup>1</sup> Emanuel (1894) stated that when he reported to the jobber that he had obtained a brown colored oleoresin from the cubeb purchased, the latter replied that, while the *United States Pharmacopœia* specified the unripe fruit, this was rarely found on the market.

<sup>2</sup> The botanical origin of this fruit is not known. Culbreth, *Materia Medica and Pharmacology* (1908), p. 138.

<sup>3</sup> The volatile oil, in part, is converted into the so-called cubeb camphor, especially when stored in a damp place. Schmidt, *Ber. d. deutsch chem. Ges.* (1877), 10, p. 188.

1860

## Oleoresina Cubebae

## Oleoresin of Cubeba

Extractum Cubebae Fluidum, *Pharm.*, 1850

Take of Cubeba,<sup>1</sup> in fine powder,<sup>2</sup> liquid have passed.<sup>3</sup> Recover from twelve troyounces; this, by distillation on a water-bath,

Ether<sup>4</sup> a sufficient quantity. eighteen fluid-ounces of ether,<sup>5</sup> and

Put the Cubeba into a cylindrical expose the residue, in a capsule, until percolator,<sup>6</sup> press it moderately, and the remaining ether has evaporated.<sup>7</sup> gradually pour Ether upon it until Lastly keep the oleoresin in a well-stopped bottle.<sup>8</sup>

1870

## Oleoresina Cubebae

## Oleoresin of Cubeba

Take of Cubeba,<sup>1</sup> in fine powder,<sup>2</sup> ed.<sup>3</sup> Recover the greater part of the twelve troy-ounces; ether by distillation on a water-bath,<sup>4</sup>

Ether<sup>5</sup> a sufficient quantity. and expose the residue, in a capsule,

Put the Cubeba into a cylindrical until the remaining ether has evaporated.<sup>7</sup> When, after standing in a close percolator, provided with a stop-cock, vessel, the liquid has deposited a waxy and arranged with a cover and receptacle suitable for volatile liquids,<sup>6</sup> and crystalline matter, decant the press it moderately, and gradually oleoresin<sup>8</sup> and keep it in a well-stopped bottle.<sup>9</sup>

fluidounces of liquid have slowly pass-

1880

## Oleoresina Cubebae

## Oleoresin of Cubeba

Cubeba,<sup>1</sup> in No. 60 powder,<sup>2</sup> one hundred parts .....100

Stronger Ether,<sup>3</sup> a sufficient quantity. tillation on a water-bath,<sup>4</sup> and expose the residue, in a capsule, until the remaining ether has evaporated.<sup>5</sup>

Put the Cubeba into a cylindrical Transfer the remainder to a close vessel, and let it stand until it ceases to deposit a waxy and crystalline matter. Lastly, pour off the oleoresin.<sup>8</sup> Keep the oleoresin in a well-stopped bottle.<sup>9</sup>

liquid have slowly passed.<sup>6</sup> Recover Preparation: Trochisci Cubebae.

the greater part of the ether by dis-



1890

## Oleoresina Cubebae

## Oleoresin of Cubeb

Cubeb,<sup>1</sup> in No. 30 powder,<sup>2</sup> *five hundred grammes* .....500 Gm. *distillation on a water-bath,\* and, having transferred the residue to a capsule, allow the remaining ether to*  
 Ether,<sup>3</sup> *a sufficient quantity.* *evaporate spontaneously.'*

Put the Cubeb into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and receptacle suitable for volatile liquids.<sup>4</sup> Press the drug firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted.<sup>5</sup> Recover the greater part of the ether from the percolate by

Keep the product in a well-stoppered bottle.<sup>6</sup>

NOTE. Oleoresin of Cubeb deposits, after standing for some time, a waxy and crystalline matter, which should be rejected, only the liquid portion being used.<sup>7</sup>

Preparation: Trochisci Cubebae.

1900

## Oleoresina Cubebae

## Oleoresin of Cubeb

Cubeb,<sup>1</sup> in No. 30 powder,<sup>2</sup> *five hundred grammes* .....500 Gm. *maining alcohol to evaporate, with constant stirring, in a warm place.'*  
 Alcohol,<sup>3</sup> *a sufficient quantity.* *Keep the oleoresin in a well-stoppered bottle.'*

Introduce the cubeb into a cylindrical glass percolator,<sup>4</sup> pack the powder firmly, and percolate slowly with alcohol, added in successive portions, until the cubeb is exhausted.<sup>5</sup> Recover the greater part of the alcohol from the percolate by distillation on a water-bath,<sup>6</sup> and, having transferred the residue to a dish, allow the re-

NOTE. Oleoresin of cubeb deposits, after standing for some time, a waxy and crystalline matter, which should be rejected, the liquid portion only being used.<sup>7</sup>

Average dose. — 0.500 Gm. = 500 milligrammes (7½ grains.)

1910

## Oleoresina Cubebae

## Oleoresin of Cubeba

## Oleores. Cubeba

Cubeba,<sup>1</sup> in No. 30 powder,<sup>2</sup> *five hundred grammes* ..... 500 Gm.  
Alcohol,<sup>3</sup> *a sufficient quantity*.

Place the cubeba in a cylindrical glass percolator,<sup>4</sup> pack the powder firmly, and percolate slowly with alcohol, added in successive portions, until the drug is exhausted.<sup>5</sup> Recover the greater part of the alcohol from the percolate by distillation on a water-bath,<sup>6</sup> and, having transferred the residue to a dish, allow the remaining

alcohol to evaporate, in a warm place, stirring frequently.<sup>7</sup> Keep the oleoresin in a well stoppered bottle.<sup>8</sup>

NOTE—Oleoresin of Cubeba, after standing for some time, deposits a waxy and crystalline precipitate, which should be rejected, the liquid, portion only being used.<sup>9</sup>

Preparation—Trochisci Cubebae.

Average Dose—Metric, 0.5 Gm.—Apothecaries, 8 grains.

1) For a description of the drug, see page 1040 under "Drug used, its collection, preservation, etc."

2) The last three editions of the Pharmacopœia have specified that the drug used be reduced to a No. 30 powder for percolation. Previous editions, with the exception of that of 1850, directed that a fine powder (No. 60) be used for this purpose. In the Pharmacopœia of 1850, the degree of fineness was not specified. The coarser powder corresponds more nearly in its composition to that of the whole fruit than does the fine powder, owing to the fact that a relatively large amount of volatile oil is lost in the preparation of the latter.

3) Previous to the edition of 1900, the Pharmacopœia specified the use of ether for extracting the drug, whereas, the last two editions have directed that alcohol be employed for this purpose. The fact, that the latter yields a product differing but slightly in its physical properties from the oleoresin obtained with ether, was pointed out by Procter in 1866, and later confirmed by other investigators. Since the alcoholic preparation appears to be equally as efficient from a therapeutic standpoint, as well, the change from ether to alcohol appears to be justified. The use of a menstruum consisting of equal parts of alcohol and ether, as specified in some of the foreign pharmacopœias, the Austrian, German and Japanese,

does not appear to offer any special advantage either from a pharmaceutic or therapeutic standpoint.

4) In the Pharmacopœias of 1870, 1880 and 1890, the drug was directed to be extracted in a percolator specially adapted to the use of volatile solvents. See Part I under "Apparatus used." With the change in menstruum (ether to alcohol), a special form of percolator was no longer necessary, and the Pharmacopœia now directs that an ordinary cylindrical, glass percolator be used.

5) In the earlier editions of the Pharmacopœia (1850 to 1880 inclusive), it was directed that percolation be discontinued short of the complete exhaustion of the drug, the object evidently having been to economize in the use of the relatively expensive solvent, ether. With the reduction in the price of the latter, however, the economic factor diminished in importance and as a result the Pharmacopœia of 1890 directed that percolation be allowed to proceed until the drug was exhausted. This is also the procedure given in the more recent editions of the Pharmacopœia, in which alcohol has replaced ether as the extracting menstruum.

In this connection, it is desired to point out that, whereas percolation, when ether is the menstruum used, should be continued to complete exhaustion of the drug in order that the extraction of the total amount of therapeutically active constituents may be assured, this procedure does not appear to be necessary when alcohol is the solvent employed. While this statement is not in conformity with the present pharmacopœial directions governing the extraction of the drug and is not supported by direct experimental evidence, it is thought to be justified in view of the difference in the solubility of the therapeutically active resins in the above mentioned menstrua. The indifferent resin is but slightly soluble in ether. It will, therefore, be extracted but slowly by this solvent and will be present in the percolate even to the last portions. Alcohol, on the other hand, dissolves both, the acid and indifferent resins readily. These substances should therefore be contained *in toto* in the first portions of the percolate. In this case, it would therefore appear that the continuation of the process of extraction to the complete exhaustion of the drug

only serves to load the percolate with undesirable extractive matter such as cubebin.

6-7) The various editions of the Pharmacopœia, since 1870, have directed that the greater part of the solvent be removed from the percolate by distillation on a water bath, and that the remainder be allowed to evaporate spontaneously.

Experience in the laboratory has shown that it is impossible to obtain a uniform product, when operating according to the above directions, unless identical conditions are maintained in each case. This is due to the fact that a comparatively slight variation in the procedure, with respect to the quantity of the solvent removed by distillation or to the temperature at which spontaneous evaporation is allowed to proceed produces a variation in the volatile oil content of the finished product, which in turn affects its physical and chemical properties. It is thought, therefore, that the amount of solvent to be removed by distillation, as well as the temperature at which the last portions are to be removed, should be definitely stated by the Pharmacopœia in order that a more uniform product may be obtained.

8) For a statement concerning the nature of the precipitate which forms in the oleoresin upon standing, see page 1060 under "Other properties."

Since the greater part of the precipitate is composed of material which is of no therapeutic value, it should be removed before dispensing the preparation as directed by the Pharmacopœia.

9) The oleoresin should be kept in well stoppered bottles owing to the fact that it loses volatile oil and undergoes other changes on exposure to the air. See cubeb camphor, page 1050.

### *Yield*

The amount of oleoresin obtained varies to a considerable extent, 10 to 30 per cent, having been obtained when alcohol, acetone or ether were employed as menstrua for the extraction of the drug. When petroleum ether is the solvent made use of, the yield is much lower, 4 to 18 per cent. having been reported in this case. -Aside from the effect of the solvent, the principal

factors influencing the yield appear to be the variation in the volatile oil content of the drug from which the oleoresin is prepared and the conditions under which the preparation of the latter has been accomplished. As the volatile oil content of the cubeb fruit is stated to vary from 10 to 18 per cent., a variation of even greater magnitude is to be expected in the amount of oleoresin obtained. While this is true when a vacuum pan is employed in the evaporation of the solvent, the difference is not so great when the pharmacopœial directions are followed as the loss in volatile oil in this case is relatively greater when the fruits contain a large amount of this constituent than when only a small amount is present. The difference is still further decreased when the solvent is evaporated on a water bath under ordinary atmospheric pressures. The following tables show the yield of oleoresin obtained with the use of various solvents:

TABLE 47 — *Yield of oleoresin as reported in the literature.*

Date	Observer	Yield of oleoresin to—				Remarks
		Alco- hol	Acce- tone	Ether	Other solvents	
		Per cent	Per cent	Per cent	Per cent.	
1846	Bell.....			15.0 to 20.0		
1868	Procter .....	27.00		21.90	Benzin 16.50	
1867	Pile .....				Benzin 5.00	Yield to benzin, sp. gr. 86° Baumé.
1868	Heydenreich .....			23.75	Gasolin 16.50	
1877	Griffin .....				16.50	
1887	Kremel .....	30.00		22.00	Benzin 16.65	
1888	Trimble.....			21.26		
1892	Berlinger.....		21.75			} The cubebs were completely exhausted.
			24.10			
			25.00			
1892	Sherrard.....			16.40		
				18.80		
				21.06		
				21.90		
				23.00		
				24.70		
				24.80		
				24.80		
1895	Hyers.....	14.48	18.48	22.45	Petrol. Ether. 13.47	
1907	Blome.....				Solvent(?) 18.85 to 26.88	Reported as yield of oleoresin. Results obtained in the ex- traction of 5 samples of cubebs.
1907	Evans Sons, Lescher & Webb .....				22.08 22.60 21.13 22.80	
1908	Vanderkleed .....				Solvent(?) 13.66 to 23.60	Reported as yield of oleoresin. Results obtained in the ex- traction of 4 samples of cubebs.
1909					Solvent(?) 16.49 to 24.34	Reported as yield of oleoresin.
1910	Southall Bros., & Barclay.....				Petrol Ether 3.88 4.80 4.45 14.00 16.03 16.54 16.90 18.08	On subsequent extraction with alcohol 3.40 to 5.66 per cent. of extractive matter was ob- tained.
1910	Vanderkleed .....				Solvent(?) 18.42 to 24.40	Reported as yield of oleoresin. Results obtained in the ex- traction of 6 samples of cubebs.
1911	Vanderkleed .....				Solvent(?) 22.14	Reported as yield of oleoresin.
1911	Southall Bros. & Barclay.....				Petrol Ether 4.66 to 8.78	The average yield of 5 samples of cubebs is given as 6.95.

TABLE 47—*Yield of oleoresin as reported in the literature—Continued.*

Date	Observer	Yield of oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Other solvents	
		Per cent	Per cent	Per cent	Per cent.	
1912	Vanderkleed ....				Solvent(?) 17.36 to 24.49	Reported as yield of oleoresin. Results obtained in the extraction of 5 samples of cubebs.
1913	Dohme & Engelhardt.....				Solvent(?) 16.00 to 22.00	Reported as yield of oleoresin.
1913	Vanderkleed ....				Solvent(?) 21.18	
1914	Riedel.....				Alcohol and ether 11.10 to 14.70	
1914	Rippetoe.....	8.87 to 11.04		7.68 to 9.80		Results obtained in the extraction of 6 samples of cubebs. Reported as anhydrous extracts.
1914	Scoville.....				Solvent(?) 18.10 to 22.00	Reported as yield of oleoresin.
1914	Vanderkleed ....				Solvent(?) 13.90 to 19.80	Reported as yield of oleoresin. Results obtained in the extraction of 6 samples of cubebs.

TABLE 48—*Yield of oleoresin as obtained in the laboratory.*

Date	Observer	Yield of oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Other solvents	
		Per cent	Per cent	Per cent	Per cent.	
1910	DuMez & Netzel.	27.09	26.07	23.47	Benzin 18.75	Represents the yield using a Soxhlet's extraction app., except in the case of alcohol.
1916	DuMez.....	16.34	16.76.	15.28	Petrol Ether 13.04	Represents the yield using a Soxhlet's extraction app., except in the case of alcohol.

*Chemistry of the Drug and Oleoresin.**Tabulation of Constituents.*

We are indebted principally to Bernatzik<sup>1</sup> Schmidt<sup>2</sup> and Schulze<sup>3</sup> for definite information concerning the constituents of the cubeba fruit. According to these investigators, the constituents of importance from a pharmaceutical standpoint are as follows: volatile oil, fatty oil, fat, cubebin, cubebic acid, indifferent resin, coloring matter, starch, gum and inorganic substances. Inasmuch as an attempt to determine the composition of the oleoresin does not appear to have been made since the identification of the above enumerated constituents, a definite statement concerning its exact composition can not be given.<sup>4</sup> However, a knowledge of the physical properties of the constituents of the fruit warrants the statement that the following are present in the oleoresin when prepared with alcohol or ether:

Volatile oil	Cubebin	Coloring matter
Fatty oil	Cubebic acid (Acid resin)	Ash
Fat	Resin (Indifferent resin)	

*Occurrence and Description of Individual Constituents*

**Volatile Oil.**<sup>5</sup> The volatile oil of cubeba is a colorless or pale green, thick fluid possessing a burning, spicy, but not a bitter taste. Its specific gravity varies (0.915 to 0.937 at 15°C) depending on the age of the oil after distillation or the length of time that the fruits have been stored before obtaining the oil. It is strongly refractive and is laevogyrate,—39.45° to

<sup>1</sup> Buchner's n. Repert. f. d. Pharm. (1865), 14, p. 97.

<sup>2</sup> Arch. d. Pharm. (1870), 191, p. 23.

<sup>3</sup> *Ibid.* (1873, 202, p. 388.

The following are among the early investigators who have reported analyses of the fruit: Trommsdorff, Trommsdorff's n. Journ. der Pharm. (1811), 20, p. 69; Vauquelin, Journ. de Chim. Med. (1820), 21, p. 103; Taschenb. f. Scheidekuenst. (1822), p. 185; Monheim, Buchner's Repert. d. Pharm. (1833), 44, p. 199.

<sup>4</sup> Vieth in an article on the relation between the chemical composition and therapeutic activity of various balsams states that *Kubebenextrakt* consists of terpenes (25 per cent.) resin acids (10 per cent.) and resins (25 per cent.) Verh. d. Ges. deutsch. Naturf. u. Aerzte (1905), 2, p. 364.

<sup>5</sup> The above description is for the volatile oil obtained from the fruits by steam distillation and corresponds to the properties as observed by Schmidt, Arch. d. Pharm. (1870), 191, p. 18.



—40.16°. Alcohol, ether, carbon disulphide, petroleum ether, chloroform and fatty oils dissolve it readily.

The investigation of the composition of this oil has been undertaken by a number of workers.<sup>6</sup> Oglialoro<sup>7</sup> noted the presence of a small amount of a l-terpene (pinene or camphene). Wallach<sup>8</sup> isolated dipentene and cadinene. The presence of the latter has been confirmed by others.<sup>9</sup> Cubeb camphor<sup>10</sup> has also been obtained from certain samples of the oil. It is a sesquiterpene hydrate ( $C_{15}H_{24}H_2O$ ) which forms when the fruits are stored in a damp place or when the oil is exposed to a moist atmosphere. It separates out in the form of rhombic octahedrons when the oil is cooled at a low temperature (—12 to —14°C) for some time.

The yield of the oil is stated by Schimmel & Co.<sup>11</sup> to be from 10 to 18 per cent. A yield as low as 0.4 per cent. has been reported.<sup>12</sup> Schmidt obtained 14.215 per cent. from fresh cubebs and 13.041 per cent. from stored cubebs.<sup>13</sup>

*Fatty Oil.* Schmidt<sup>14</sup> describes the fatty oil as a thick, dark green liquid congealing at 0°C. It is stated to be slowly but completely soluble in cold alcohol, more soluble in hot alcohol, readily soluble in ether, chloroform, carbon disulphide and fatty oils.

The yield as reported by the above investigator is 1.175 per cent. for fresh cubebs and 1.096 per cent. for fruits which have been stored for some time.

<sup>6</sup> The earliest work on the constituents of the oil is that of Soubelran and Capitaine, *Ann. d. Chem.* (1840), 34, p. 31.

<sup>7</sup> *Gaz. Chim. Ital.* (1875), 5, p. 497.

<sup>8</sup> *Ann. d. Chem.* (1887), 238, p. 78.

<sup>9</sup> Schaer and Wyss, *Arch. d. Pharm.* (1875), 206, p. 216; Umney, *Pharm. Journ.* (1895), 25, p. 951.

<sup>10</sup> Blanchet and Sell, *Ann. d. Chem.* (1833), 6, p. 294; Winckler, *Buchner's Repert. f. d. Pharm.* (1833), 45, p. 397; Bernatzik, *Buchner's n. Repert. f. d. Pharm.* (1865), 14, p. 97; Schmidt, *Ber. d. deutsch. chem. Ges.* (1877), 10, p. 188.

<sup>11</sup> Schimmel & Co., *Ber.* (1897), p. 14.

<sup>12</sup> Busse reports the yield of volatile oil as obtained by various investigators as follows:

Baumé .....	5.3 per cent.
Schoenwald .....	7.03 per cent.
Oberdoerffer .....	12.5 per cent.
Hager .....	0.4 per cent.
Busse .....	15. per cent.

*Arch. d. Pharm.* (1844), 89, p. 30.

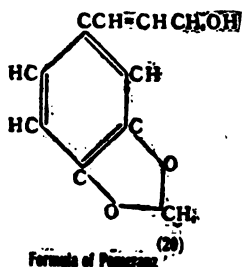
<sup>13</sup> *Ibid.* (1870), 191, p. 18.

<sup>14</sup> *Ibid.*, p. 34.

**Fat.** Schmidt<sup>15</sup> obtained 0.511 per cent. of a semi-solid fat from fresh cubebs, 0.408 per cent. from old cubebs. It is stated to be of ointment-like consistence, melting at 30 to 32°C. Hot alcohol, ether, carbon disulphide, chloroform, benzene and petroleum ether dissolve it readily. It is reported to be insoluble in cold alcohol.

**Cubebin.**<sup>16</sup> Cubebin crystallizes from alcohol in white, odorless needles melting at 125 to 126°C (Schmidt),<sup>17</sup> 132°C (Mameli).<sup>18</sup> The alcoholic solution has a bitter taste. It is only slightly soluble in cold alcohol, quite soluble in hot alcohol, readily soluble in ether, chloroform, carbon disulphide, glacial acetic acid, fatty and volatile oils. The chloroformic solution is laevogyrate. Concentrated sulphuric acid dissolves it with a purple violet color, a reaction which is used as test for the identity of the cubeb fruit and the oleoresin prepared therefrom.

Cubebin was thought by Heldt<sup>19</sup> to be an oxidation product of the sesquiterpene constituent of the volatile oil,  $2 C_{15}H_{24} + 18 O = C_{30}H_{20}O_9 + 9 H_2O$ . Later work on the determination of its structure, however, has shown this theory to be untenable. The following structural formulas have been brought forward to represent its composition.



<sup>15</sup> *Ibid.*

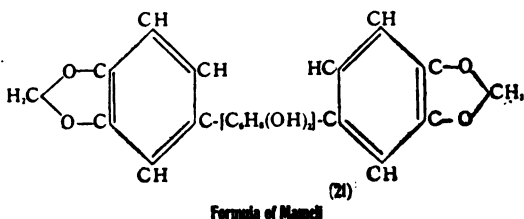
<sup>16</sup> Monheim, Buchner's Repert. f. d. Pharm. (1833), 44, p. 199; Cassola, Journ. d. Chim. Med. (1834), 10, p. 685; Soubeiran and Capitaine, Journ. de Pharm. et de Chim. (1839), 25, p. 355; Ann. d. Chem. (1840), 34, p. 323; Steer, Buchner's Repert. f. d. Pharm. (1838), 11, p. 88; *Ibid.* (1840), 20, p. 119; Schuck, Buchner's n. Repert. f. d. Pharm. (1852), 1, p. 213; Engelhardt, *Ibid.* (1854), 3, p. 1; Bernatzik, *Ibid.* (1865), 14, p. 97; Schmidt, Arch. d. Pharm. (1870), 191, p. 1; Weidel, Wien. Akad. Ber. (1878), 74, p. 377.

<sup>17</sup> *L. c.*

<sup>18</sup> Chem. Ztg. (1908), 32, p. 46.

<sup>19</sup> Arch. der Pharm. (1870), 191, p. 23.

<sup>20</sup> Monatsch. f. Chem. (1888), 9, p. 323.



Cubebin occurs in the fruit to the extent of about 2.5 per cent.<sup>22</sup>

*Cubebic Acid. (Acid Resin)* Cubebic acid,  $C_{18}H_{14}O_{11}$  (Schmidt),<sup>23</sup>  $C_{28}H_{30}O_7 \cdot H_2O$  (Schulze),<sup>24</sup> was first described by Bernatzik. It is a white, resinous mass melting at  $56^\circ C$  (Schmidt),  $45^\circ C$  (Schulze) and becoming brown on exposure to the air. It shows only a weak acid reaction. Alcohol, ether, ammonia and the caustic alkalis dissolve it readily.

There is a considerable variation in the cubebic acid content of the fruit as reported in the literature. Schmidt<sup>25</sup> obtained 0.96 per cent. from fresh cubebs and 1.16 per cent. from the fruit which had been stored. Bernatzik reports the presence of 3.458 per cent.<sup>26</sup>

*Resin.* The so-called indifferent resin,  $C_{13}H_{14}O_5$  (Schmidt)<sup>27</sup> is a yellowish-brown, pulverulent mass readily soluble in alcohol and the caustic alkalis, but only slightly soluble in ether, chloroform and carbon disulphide.

The indifferent resin occurs in the fruit to the extent of about 3 per cent. on the average.<sup>28</sup>

*Coloring Matter.* Schmidt<sup>29</sup> isolated a brown amorphous substance to which he attributes the brown color. This substance is stated to be soluble in dilute alcohol and solutions of the alkali-

<sup>22</sup> l. c.

<sup>23</sup> Monheim obtained 4.5 per cent. of a resin resembling piperine which he designated *cubebin*. Buchner's Repert. f. d. Pharm. (1833), 44, p. 199.

Schmidt reports the presence of 2.484 per cent. in fresh cubebs and 2.576 per cent. in cubebs kept in storage for some time. l. c.

<sup>24</sup> l. c.

<sup>25</sup> Arch. d. Pharm. (1879), 202, p. 388.

<sup>26</sup> l. c.

<sup>27</sup> Buchner's n. Repert. f. d. Pharm. (1865), 14, p. 97.

<sup>28</sup> l. c.

<sup>29</sup> Schmidt observed the presence of 2.258 per cent. of indifferent resin in the fresh fruits, 2.968 per cent. in stored fruits, l. c.

Bernatzik obtained 3.515 per cent. of this resin, l. c.

<sup>30</sup> l. c.

lies. The green color of the fatty oil as observed by the same investigator is stated to be due to chlorophyll.

*Ash.* According to E. Schmidt,<sup>30</sup> the ash of the cubeba fruit is composed of the basic elements, K, Ca, Mg, and Fe in combination with the acid radicles Cl', SO<sub>4</sub>", PO<sub>4</sub>""', CO<sub>3</sub>" and SiO<sub>3</sub>""', also free SiO<sub>2</sub>.

Cubeba fruits yield about 5.5 to 6.0 per cent. of ash.<sup>31</sup>

#### *Constituents of Therapeutic Importance.*

The value of the oleoresin of cubeba as a therapeutic agent is very probably due to its resin content. In addition to its diuretic action, the acid resin is said to render the urine feebly antiseptic and to act as an astringent.<sup>1</sup> Cubebin has been shown to be physiologically inactive passing through the intestines unabsorbed.<sup>2</sup> The volatile oil is stated to act merely as a carminative<sup>3</sup> and its presence is even considered by some to be undesirable<sup>4</sup> owing to its irritating action.

#### *Physical Properties*

*Ash.* According to E. Schmidt,<sup>30</sup> the ash of the cubeba fruit is directed by the *United States Pharmacopæia* has a grass-green color when spread out in a thin layer on a white porcelain surface. The commercial product, however, is often brownish-green or brown in color due to the use of the ripe fruit<sup>5</sup> in its manufacture. In such cases, the desired green color is sometimes imparted to the preparation by the addition of copper salts.<sup>6</sup>

*Odor:* The oleoresin has a strong aromatic odor like that of the crushed cubeba fruit. In fact, the odor is so strongly aromatic that unevaporated solvent (alcohol), even when present in considerable amounts, cannot be detected by the sense of smell.

<sup>30</sup> Arch. d. Pharm. (1870), 191, p. 11.

<sup>31</sup> Schmidt obtained only 3.36 per cent of ash, l. c.

Warnecke reports the yield of ash as 5.45 per cent. Pharm. Ztg. (1886), 31, p. 536.

LaWall and Bradshaw give the ash content of two samples of cubeba as 5.70 and 6.10 per cent., respectively. Proc. A. Ph. A. (1910), 58, p. 751.

<sup>1</sup> Vieth, Med. Klin. (1905), p. 1276.

<sup>2</sup> Heffter, Arch. f. Exp. Path. u. Pharm. (1895), 35, p. 371.

<sup>3</sup> Heydenreich, Am. Journ. Pharm. (1868), 40, p. 42.

<sup>4</sup> Bernatzik, Buchner's neues Repert. (1865), 14, p. 97.

<sup>5</sup> See under "Drug used, its collection, preservation, etc."

<sup>6</sup> Bédall (1894).

**Taste:** The taste is bitter and somewhat spicy, like that of cubeb, only more pronounced.

**Consistence:** The oleoresin is, as a rule, a rather thin liquid when compared with the other members of this class of preparations. Its consistence, however, varies to a considerable extent owing to a difference in the volatile oil content.<sup>1</sup> Some of the preparations examined in the laboratory were so thick that they could only be poured with difficulty.

**Solubility:** The official preparation forms clear or slightly cloudy solutions with alcohol, acetone, ether, chloroform, carbon disulphide, and glacial acetic acid. It is almost completely soluble in petroleum ether. The solubility of the European product, which is usually prepared with a mixture consisting of equal parts of alcohol and ether, is about the same.

**Specific gravity:** The oleoresins prepared in the laboratory in 1916 showed a specific gravity of 0.99 + at 25° C regardless of whether the solvent employed in extracting the drug was alcohol, acetone or ether. The uniformity is attributed to the fact that particular pains were taken to evaporate the solvent under the same conditions in each case, thereby insuring approximately the same volatile oil content for each of the finished preparations. The variation in specific gravity due to a difference in volatile oil content is shown in the data given for the first four of the laboratory preparations. The commercial samples examined also show a variation due to this influence, except, in the case of the low specific gravity observed by Procter, which was stated to be due to the presence of unevaporated solvent (ether). Tables illustrating these points follow:

TABLE 49—*Specific gravities of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Specific gravity
				At 76° F
1.....	1866	Procter .....	Alcohol .....	0.985
2.....	"	" .....	Ether .....	0.967
3.....	"	" .....	Benzin.....	0.932
				At 25° C
1.....	1910	DuMez & Netzel.....	Alcohol .....	0.990
2.....	"	" .....	Acetone.....	0.994
3.....	"	" .....	Ether .....	0.985
1.....	1916	DuMez .....	Alcohol .....	1.048 (1)
2.....	"	" .....	" .....	0.994
3.....	"	" .....	Acetone.....	0.999
4.....	"	" .....	Ether .....	0.993
5.....	"	" .....	Petrol. ether.....	0.963

<sup>1</sup> A thick preparation containing only 4.71 per cent. of volatile matter.

<sup>1</sup> See under "Chemistry of the drug and the oleoresin".

TABLE 50.—*Specific gravities of commercial oleoresins.*

Sample No.	Date	Observer	Source	Specific gravity
1....	1886	Procter.....	Not given.....	At 76° F. 0.900 <sup>(1)</sup>
1.....	1916	DuMez.....	Lilly & Co.....	At 25° C. 0.968
2.....	"	".....	Squibb & Sons.....	0.969
3.....	"	".....	Parke, Davis & Co.....	0.971
4.....	"	".....	Sharp & Dohme.....	0.975
5.....	"	".....	Stearns & Co.....	1.017

<sup>1</sup> Contained ether.

**Refractive index:** The results obtained in the laboratory indicate that the refractive index of the oleoresin should be about 1.499 when determined at 25°C. The solvent employed in extracting the drug appears to have little influence on this constant, except in case petroleum ether is used, when it is slightly lower. The effect due to variation in volatile oil content is but slight as is shown in the tables which follow:

TABLE 51.—*Refractive indices of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Refractive index
				At 25° C
1.....	1910	DuMez & Netzel.....	Alcohol .....	1.495
2.....	"	".....	Acetone.....	1.499
3.....	"	".....	Ether.....	1.499
1.....	1916	DuMez.....	Alcohol.....	1.502 <sup>(1)</sup>
2.....	"	".....	Alcohol.....	1.500
3.....	"	".....	Acetone.....	1.500
4.....	"	".....	Ether.....	1.499
5.....	"	".....	Petrol ether.....	1.495

<sup>(1)</sup> Low in volatile oil content.TABLE 52.—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
				At 25° C
1.....	1916	DuMez.....	Lilly & Co.....	1.498
2.....	"	".....	Squibb & Sons.....	1.499
3.....	"	".....	Parke, Davis & Co.....	1.499
4.....	"	".....	Sharp & Dohme.....	1.499
5.....	"	".....	Stearns & Co.....	1.501

*Chemical Properties.*

*Loss in weight on heating:* An examination of the tables which follow shows that the oleoresin usually loses between 20 and 40 per cent. on heating at 100 to 110°C, the variation being due to the difference in the volatile oil content. The relatively small loss in weight observed in the case of four of the laboratory preparations is to be attributed to the removal of a part, or the whole, of the more volatile constituents of the essential oil in the process of evaporating the solvent. The comparatively great loss noted for two of the commercial samples is thought to have been due to the presence of unevaporated solvent. The results obtained in the determinations made in the laboratory as well as those reported in the literature are given in the tables which follow:

TABLE 53.—*Laboratory preparations—loss in weight on heating.*

Sample No.	Date	Observer	Solvent	Per cent of loss on drying
1 .....	1887	Kremel .....	Alcohol .....	At 100° C 20.40
1 .....	1916	DuMez .....	Alcohol .....	At 110° C 23.06
2 .....	"	" .....	Acetone .....	24.10
3 .....	"	" .....	Ether .....	25.88
4 .....	"	" .....	Petrol. ether .....	25.24
5 .....	"	" .....	Alcohol .....	11.90
6 .....	"	" .....	Acetone .....	9.96
7 .....	"	" .....	Ether .....	8.81
8 .....	"	" .....	Alcohol .....	4.71

TABLE 54.—*Commercial oleoresins—loss in weight on heating.*

Sample No.	Date	Observer	Source	Per cent of loss on drying
1 .....	1893	Dieterich .....	Germany .....	At 100° C 32.70
1 .....	1894	" .....	" .....	31.02
1 .....	1895	" .....	" .....	20.90
1 .....	1905	" .....	" .....	55.91 <sup>(1)</sup>
1 .....	1916	DuMez .....	Sharp & Dohme .....	At 110° C 30.72
2 .....	"	" .....	Stearns & Co. ....	31.68
3 .....	"	" .....	Parke, Davis & Co. ....	37.03
4 .....	"	" .....	Lilly & Co. ....	44.21 <sup>(1)</sup>
5 .....	"	" .....	Squibb & Sons .....	61.96 <sup>(1)</sup>

<sup>1</sup> Probably contained unevaporated solvent (alcohol).

*Ash content:* The ash content of the oleoresin varies with the solvent employed in its preparation as is shown in the first of the tables which follow. The highest values were obtained for the official product, in the preparation of which alcohol was the solvent used. The comparatively low ash content obtained for the commercial samples examined, while suggesting the use of some other solvent in the manufacture of these preparations, is thought to have been due to the greater amount of volatile matter (essential oil) present. Although copper was detected in the ash of all of the commercial products, the quantities present were too small to effect the value of this constant to any considerable extent. The following tables give the ash content of the oleoresin as reported in the literature and as determined in the laboratory:

TABLE 55.—*Ash contents of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Per cent of ash
1.....	1916	DuMez .....	Alcohol .....	0.45
2.....	"	" .....	Acetone .....	0.20
3.....	"	" .....	Ether .....	0.13
4.....	"	" .....	Petrol, ether.....	0.07
5.....	"	" .....	Alcohol .....	0.48
6.....	"	" .....	Acetone .....	0.22
7.....	"	" .....	Ether .....	0.15
8.....	"	" .....	Alcohol .....	0.51

TABLE 56—*Ash contents of commercial oleoresins.*

Sample No.	Date	Observer	Source	Per cent. of ash	Foreign constituents
1.....	1893	Dieterich ...	Germany .....	0.50	Copper
1.....	1894	" .....	" .....	0.52	
1.....	1895	" .....	" .....	0.47	
1.....	1897	" .....	" .....	0.10	
1.....	1905	" .....	" .....	0.87	
1.....	1916	DuMez .....	Squibb & Sons .....	0.21 <sup>(1)</sup>	
2.....	"	" .....	Sharpe & Dohme .....	0.40	
3.....	"	" .....	Parke, Davis & Co.....	0.35	
4.....	"	" .....	Lilly & Co.....	0.79 <sup>(1)</sup>	
5.....	"	" .....	Stearns & Co.....	0.37	

<sup>1</sup> Unevaporated solvent (alcohol) probably present.

*Acid number:* The acid numbers of the oleoresins prepared in the laboratory varied from 21.8 to 26.7, depending on the nature of the solvent employed in their preparation. The num-



ber, 26.7, obtained in the case of the preparation made with alcohol agrees very well with that (26.2) obtained by Kremel for the oleoresin when prepared in a like manner. The low acid numbers obtained for the commercial samples are explained by the presence of relatively large amounts of volatile matter (generally essential oil, but unevaporated solvent in two cases) in these preparations, which has the effect of reducing the concentration of the free acids. The values obtained for this constant follow:

TABLE 57.—*Acid numbers of laboratory preparations.*

Sample No.	Date	Observer	Solvent	Acid number
1.....	1887	Kremel .....	Alcohol .....	26.2
2.....	"	" .....	Ether .....	31.2
1.....	1916	DuMez .....	Alcohol .....	26.7
2.....	"	" .....	Acetone .....	22.8
3.....	"	" .....	Ether .....	22.2
4.....	"	" .....	Petrol. ether .....	21.8

TABLE 58.—*Acid numbers of commercial oleoresins.*

Sample No.	Date	Observer	Source	Acid number
1.....	1916	DuMez .....	Lilly & Co.....	12.8 <sup>(1)</sup>
2.....	"	" .....	Squibb & Sons .....	13.4 <sup>(1)</sup>
3.....	"	" .....	Stearns & Co.....	14.4
4.....	"	" .....	Parke, Davis & Co.....	15.4
5.....	"	" .....	Sharp & Dohme .....	18.7

<sup>(1)</sup> Probably contained unevaporated solvent (alcohol).

*Saponification value:* The saponification values obtained for the oleoresins prepared in the laboratory showed a slight variation due to the nature of the solvent used in extracting the drug as is shown in the first of the tables which follow. As a rule, however, the difference in the volatile oil content of the oleoresin, due to a variation in the conditions under which it has been prepared, is thought to be the principal factor influencing the value of this constant, as is also brought out in the first table. In the examination of commercial samples, the presence of unevaporated solvent must be taken into considera-

tion in this connection. The results obtained in the determination of this constant in the laboratory follow:

TABLE 59.—*Saponification values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Saponification value
1.....	1916	DuMez .....	Alcohol.....	65.9
2.....	"	" .....	Acetone.....	63.7
3.....	"	" .....	Ether.....	63.4
4.....	"	" .....	Petrol, ether.....	67.0
1.....	"	" .....	Alcohol.....	63.9
2.....	"	" .....	Acetone.....	57.9
3.....	"	" .....	Ether.....	59.5
1.....	"	" .....	Alcohol.....	105.9 <sup>(1)</sup>

<sup>1</sup> This preparation contained a relatively small amount of volatile matter (principally essential oil). See page 1066 under "Loss in Weight on Drying".

TABLE 60.—*Saponification values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Saponification value
1.....	1916	DuMez .....	Lilly & Co.....	48.5 <sup>(1)</sup>
2.....	"	" .....	Parke, Davis & Co.....	53.3
3.....	"	" .....	Squibb & Sons.....	49.3 <sup>(1)</sup>
4.....	"	" .....	Sharp & Dohme.....	55.0
5.....	"	" .....	Stearns & Co.....	65.9

<sup>(1)</sup> Unevaporated solvent (alcohol) probably present.

*Iodine value:* Further observations are necessary before a definite statement can be made as to what the iodine value of this preparation should be. Determinations made in the laboratory appear to indicate that it is influenced largely by the volatile oil content as those preparations which lost the greatest amount on drying usually gave the highest values for this constant. Apparent exceptions to this rule are to be found in the samples obtained from Lilly & Company and Squibb & Sons, respectively. In these cases, unevaporated solvent (alcohol) is thought to have been present, although, it could not be detected by the odor. The following tables show the values obtained for the preparations examined in the laboratory.

TABLE 61—Iodine values of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Iodine value
1.....	1916	DuMez.....	Alcohol.....	126.0
2.....	"	".....	Acetone.....	131.6
3.....	"	".....	Ether.....	138.5
4.....	"	".....	Petrol, ether.....	141.8
1.....	"	".....	Alcohol.....	130.0
2.....	"	".....	Acetone.....	113.2
3.....	"	".....	Ether.....	115.6
1.....	"	".....	Alcohol.....	92.0

TABLE 62—Iodine values of commercial oleoresins.

Sample No.	Date	Observer	Source	Iodine value
1.....	1916	DuMez.....	Squibb & Sons.....	130.6 <sup>1</sup>
2.....	"	".....	Lilly & Co.....	136.7 <sup>1</sup>
3.....	"	".....	Parke, Davis & Co.....	146.9
4.....	"	".....	Sharp & Dohme.....	147.3
5.....	"	".....	Stearns & Co.....	147.6

<sup>1</sup> Unevaporated solvent probably present.

### Other Properties.

The oleoresin, upon long standing, forms a white deposit consisting of cubebin, indifferent resin, cubebic acid and thickened oil. As the greater part (80 per cent.)<sup>1</sup> of this precipitated material consists of the therapeutically inert cubebin,<sup>2</sup> the *United States Pharmacopæia* directs that it be removed before dispensing the preparation.

### Special Qualitative Tests.

The methods which have been devised for the identification of this oleoresin or as a test for its quality are based on the fact that characteristic color changes are produced when it is acted upon by certain acids. Sulphuric, sulphomolybdic<sup>3</sup> and

<sup>1</sup> Schmidt (1870).

<sup>2</sup> See under "Constituents of therapeutic importance".

<sup>3</sup> Dieterich, in 1897, pointed out that sulphomolybdic acid might be used in place of sulphuric acid. The resulting color, however, was stated to be a cherry-red instead of a blood-red.

hydrochloric<sup>1</sup> acids have been made use of in this connection, the first mentioned being the reagent most generally employed.

Attention was first called to the value of sulphuric acid in the identification of this preparation by Kremel in 1887. He, however, reported nothing definite, merely stating that a carmine-red color was produced when the "strong" acid and oleoresin were mixed. It was not until ten years later (1897), when the firm of Dieterich in Helfenberg published their method of procedure, that this test assumed a definite form. The test as carried out by this firm is typical of those in use at the present time and is as follows:

Upon mixing 0.01 gram of the oleoresin with 3 to 5 drops of concentrated sulphuric acid, the mixture should assume an intense blood-red color.<sup>2</sup>

The fact that certain constituents of the cubeb fruit, namely, cubebin, the acid resin (cubebic acid) and the indifferent resin, formed red colored mixtures with sulphuric acid was noted by Schmidt in 1870. These observations have been confirmed in this laboratory in so far as they pertain to the production of a red color. It was further noted, however, that the shade of red varies with the particular constituent under consideration, the cubebin giving rise to a mixture which is brownish-red in color, whereas, the color is bright red (carmine-red) in the case of the acid or indifferent resin. As all of the above mentioned constituents are normally present in the oleoresin, the particular shade of red (blood-red) obtained in this test must be due to the blending of the colors produced by the action of the acid on the several constituents, and cannot be caused by the action of the acid on the cubebin, alone, as is usually reported in the literature.

As the shade of red obtained will naturally vary with the relative quantities of the several constituents present, this test not only serves as a means of identification, but is also of value in determining roughly the quality of the preparation as well.<sup>3</sup> Thus, a bright red color obtained by the action of the acid may

<sup>1</sup> Test of Gluecksmann. See the following pages.

<sup>2</sup> The so-called false cubebs give a dirty brown color when triturated with concentrated sulphuric acid, hence, we may expect the oleoresin prepared therefrom to form a mixture of a similar color. See *Pharm Ztg.* (1912), 84, p. 845.

<sup>3</sup> Bédall (1894) observed that the oleoresins possessing a green color gave a more intense red with sulphuric acid than those which were brown in color.

be taken as an indication of the presence of relatively large amounts of the therapeutically active resins, while a dark shade of red implies that the cubebin content is exceptionally large or that the resins are present in comparatively small amounts.

The test of Gluecksmann (1912) in which hydrochloric acid is the reagent made use of, appears to be based on the presence of cubebin.<sup>1</sup> It is carried out as follows:

Dissolve a small quantity (a trace) of the oleoresin in concentrated acetic acid and dilute with the latter until the solution shows scarcely any color. Heat to boiling and add 5 drops of a 35 per cent. solution of hydrochloric acid to a 5 cubic centimeter portion. A faint yellowish-brown color should appear immediately. Upon standing quietly, the color should change in 2 to 4 hours to a brownish-violet, and then to a violet blue, after which it should gradually disappear.

While the foregoing may prove to be a test of considerable worth in the identification of the oleoresin, the length of time required for its completion would appear to be a drawback to its general application.

The tests of this nature prescribed by the various pharmacopœias all involve the use of sulphuric acid. As will become apparent in the following description of these methods, the color specified differs to a considerable extent. This may be due, as already pointed out, to a variation in the relative quantities of the reacting constituents, or, as has been further observed in the laboratory, to the strength of the acid employed. A very slight dilution with water will cause the color to change from red to purple. The following are the tests prescribed by the different pharmacopœias:

*Austrian Pharmacopœia (1906)*: The oleoresin should give a red color on being triturated with concentrated sulphuric acid.

*French Pharmacopœia (1908)*: The oleoresin should give a purple-red color with concentrated sulphuric acid.

*Swiss Pharmacopœia (1907)*: If 0.01 to 0.02 grams of the oleoresin are mixed with a few drops of concentrated sulphuric acid, an intense brownish-red color should be produced. Upon diluting with a little water, the color should change to a rose and upon further dilution, it should disappear.

*Hungarian Pharmacopœia (1909)*: A drop of concentrated sulphuric

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<sup>1</sup> This assumption is made in view of the fact that the closely related compounds, coniferyl alcohol and syringenin, give similar color reactions with hydrochloric acid. See Euler, *Die Pflanzenchemie* (1908), Vol. I, p. 87.

acid added to a drop of the oleoresin spread out in a thin layer on a white porcelain surface should produce a blood-red mixture.

*German Pharmacopoeia (1910):* If 1 cubic centimeter of a mixture of 4 parts of concentrated sulphuric acid and 1 part of water is poured over 1 drop of the oleoresin, a red color should be produced. Upon diluting the mixture with water the color should disappear.

### *Special Quantitative Tests.*

Apparently but one attempt has been made to develop a method for the quantitative determination of the constituents of therapeutic importance in this preparation, the same having been made by Kremel in 1887. As no work of this nature was done on the oleoresin in the laboratory, and, as there is no further information on this subject in the literature, a statement cannot be made as to the value of this method. However, as a suggestion of what might be accomplished in this direction, a description of the method is included here. It is as follows:

*Kremel's Method for the Estimation of Cubebic Acid (1887):* Dissolve 3 to 5 grams of the oleoresin in 4 times the quantity of alcohol (90 per cent.), filter the solution and add alternately to the filtrate an alcoholic solution of calcium chloride and ammonia water until a distinct cloudiness appears. Set the liquid aside for a day or two to allow the calcium salt of cubebic acid to crystallize. Then, collect the precipitate on a filter, wash successively with alcohol (90 per cent.) and ether, dry at 100°C and weigh. Compute the weight of the cubebic acid using the formula,  $C_{18}H_{12}O_7Ca$ , for the calcium salt.

According to the results obtained by Kremel, the oleoresin prepared with ether showed a cubebic acid content of 2.35 per cent., while the same when prepared with alcohol gave 5.75 per cent. of cubebic acid.

### *Adulterations.*

Willful adulteration of this preparation does not appear to be practiced very extensively, although, the occasional use of fixed oils<sup>1</sup> or salts of copper<sup>2</sup> for this purpose has been reported

<sup>1</sup> Schneider and Suess, *Handkommentar zum Arzneibuch fuer das deutsche Reich* (1902), p. 376.

<sup>2</sup> Bédall (1894).

A trace of copper is usually present in the commercial preparations as a result of the use of copper utensils in their manufacture. (See under "Ash".)

in the literature. On the other hand, accidental adulteration effected through the use of ripe instead of unripe fruits in the preparation of the oleoresin is thought to be quite general. (See under "Drug used, its collection, preservation, etc.")

### OLEORESIN OF GINGER

#### *Synonyms*

- Aetherisches Ingwerextrakt*, Nat. Stand. Disp. 1884.  
*Ethereal Extract of Ginger*, King's Am. Disp., (1900), p. 1336.  
*Extractum Zingiberis aethereum*, Hirsh, Univ. P. 1902, No. 1320.  
*Extractum Zingiberis aethereum*, King's Am. Disp. (1900), P. 1336.  
*Gingerin*, Chem. and Drugg. (1913), 82, p. 470.  
*Gingerine*, Am. Journ. Pharm. (1898), 70 p. 466.  
*Oleoresina Zingiberis*, U. S. P. 1910.  
*Oléorésine de Gingembre*, U. S. Disp. 1907.  
*Piperoide du Gingembre*, Béral, 1834.  
*Piperoid of Ginger*, U. S. Disp. 1865.  
*Zingiberin*, U. S. Disp. 1907.

#### *History*

The oleoresin of ginger was prepared in 1834 by Béral, a Frenchman, but was apparently first brought to the notice of American pharmacists by Proctor in 1849. It was introduced into the *United States Pharmacopœia* in 1860 and is still official at the present time. While the oleoresin has never been officially recognized abroad, a similar preparation is said to be used extensively in England under the name of gingerin.<sup>1</sup>

#### *Drug Used, Its Collection, Preservation, Etc.*

For this drug, the present pharmacopœial definition is as follows: "The dried rhizomes of *Zingiber officinale* Roscoe (Fam. *Zingiberaceae*,) the outer cortical layers of which are often either partially or completely removed. Preserve it in tightly-closed containers, adding a few drops of chloroform or carbon tetrachloride, from time to time, to prevent attacks by insects." The official drug has also been described in the literature under the following botanical synonyms: *Amomum Zingiber* Linné, and *Zingiber Zingiber* (Linné) Rusby.

<sup>1</sup> Gingerin is stated to be the extract obtained upon evaporating off the alcohol from the tincture of ginger. Chem. & Drugg. (1913), 82, p. 470.

The rhizomes as they are found on the market occur in a variety of forms characteristic of the source from which they are obtained. In view of this fact, the Pharmacopœia recognizes six different commercial varieties, namely: Jamaica ginger, African ginger, Calcutta ginger, Calicut ginger, Cochin ginger and Japanese ginger. These commercial forms differ to a considerable extent, not only through natural causes, but also through a difference in the conditions under which they are harvested and prepared for the market.

As a rule the rhizomes are dug after the stems have withered, January or February, when one or more years old. Experience has shown the oleoresin content to be the greatest at this period of the year.<sup>1</sup> They are then washed in boiling water to prevent germination, dried rapidly in the sun, and as such constitute, what is known as black, coated, or unscrapped ginger. In other cases, after treatment with boiling water, a part or the whole of the epidermis is removed, the rhizomes dried, and bleached with sulphur fumes, chlorinated lime, milk of lime or gypsum. This constitutes the so-called, white, uncoated, scraped, race or hard ginger.<sup>2</sup>

In commenting on the relative values of these various forms of ginger in the preparation of the oleoresin, it should be stated, first of all, that the yield of oleoresin is influenced to the largest extent by habitat, African ginger giving the maximum yield.<sup>3</sup> Secondly, the extent to which the rhizomes have been decorticated is an important factor, as the outer corky layer contains none of the oleoresinous material. These factors will be more fully discussed under yield. To what degree, if at all, the process of so-called bleaching effects the yield or quality of oleoresin does not become apparent from the literature. It is thought, however, that a heavy coating of gypsum, for instance, would tend to considerably reduce the percentage of oleoresin obtainable.

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<sup>1</sup> Hooper, *Pharm. Journ.* (1912), 89, p. 391.

<sup>2</sup> Culbreth, *Mat. Med. and Pharmacol.* (1917), p. 130.

<sup>3</sup> See reference under "Yield of oleoresin".



*U. S. P. Text and Comments Thereon.*

The oleoresin of ginger first became official in the Pharmacopoeia of 1860. It has remained official throughout all of the subsequent editions.

1860

## Oleoresina Zingiberis

## Oleoresin of Ginger

Take of ginger,<sup>1</sup> in fine powder,<sup>2</sup> alcohol until twelve fluidounces<sup>3</sup> of twelve troyounces;  
Stronger Ether<sup>4</sup> twelve fluidounces; from this, by distillation on a water-bath, nine fluidounces of ether,<sup>5</sup> and Alcohol<sup>6</sup> a sufficient quantity.

Put the ginger into a cylindrical percolator,<sup>7</sup> press it firmly, and pour upon it the stronger ether.<sup>8</sup> When this has been absorbed by the powder, add expose the residue, in a capsule, until the volatile part has evaporated.<sup>9</sup> Lastly keep the oleoresin in a well-stopped bottle.<sup>10</sup>

1870

## Oleoresina Zingiberis

## Oleoresin of Ginger

Take of ginger,<sup>1</sup> in fine powder,<sup>2</sup> stronger ether.<sup>3</sup> When this has been absorbed by the powder, add alcohol twelve troyounces;  
Stronger Ether<sup>4</sup> twelve fluidounces; until twelve fluidounces of liquid have Alcohol<sup>5</sup> a sufficient quantity.

Put the ginger into a cylindrical percolator, provided with a stop-cock, and arranged with a cover and receptacle suitable for volatile liquids,<sup>6</sup> press it firmly, and pour upon it the greater part of the ether by distillation on a water-bath,<sup>7</sup> and expose the residue, in a capsule, until the volatile part has evaporated.<sup>8</sup> Lastly, keep the oleoresin in a well-stopped bottle.<sup>9</sup>

1880

## Oleoresina Zingiberis

## Oleoresin of Ginger

Ginger,<sup>1</sup> in No. 60 powder,<sup>2</sup> one hundred (100) parts ..... 100 liquid have slowly passed, or until the Ginger is exhausted.<sup>3</sup> Recover the Stronger Ether,<sup>4</sup> a sufficient quantity.

Put the ginger into a cylindrical percolator, provided with a cover and receptacle suitable for volatile liquids,<sup>5</sup> press it firmly, and gradually pour stronger ether upon it, until one hundred and fifty (150) parts of the greater part of the ether by distillation on a water-bath,<sup>6</sup> and expose the residue, in a capsule, until the remaining ether has evaporated.<sup>7</sup> Keep the oleoresin in a well-stopped bottle.<sup>8</sup>

1890

## Oleoresina Zingiberis

## Oleoresin of Ginger

Ginger,<sup>1</sup> in No. 60 powder,<sup>2</sup> *five hundred grammes* ..... 500 Gm. portions, until the drug is exhausted.<sup>7</sup>  
 Ether,<sup>3</sup> *a sufficient quantity*. Recover the greater part of the ether from the percolate by distillation on a water-bath,<sup>8</sup> and, having transferred the residue to a capsule, allow the remaining ether to evaporate spontaneously.<sup>9</sup>

Put the ginger into a cylindrical glass percolator, provided with a stop-cock, and arranged with cover and receptacle suitable for volatile liquids.<sup>5</sup> Press the drug firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted.<sup>7</sup> Recover the greater part of the ether from the percolate by distillation on a water-bath,<sup>8</sup> and, having transferred the residue to a capsule, allow the remaining ether to evaporate spontaneously.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

1900

## Oleoresina Zingiberis

## Oleoresin of Ginger

Ginger,<sup>1</sup> in No. 60 powder,<sup>2</sup> *five hundred grammes* ..... 500 Gm. is exhausted.<sup>7</sup> Recover the greater part of the acetone from the percolate by distillation on a water-bath,<sup>8</sup> and, having transferred the residue to a dish, allow the remaining acetone to evaporate spontaneously in a warm place.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

Introduce the ginger into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle suitable for volatile liquids.<sup>5</sup> Pack the powder firmly, and percolate slowly with acetone, added in successive portions, until the ginger is exhausted.<sup>7</sup> Recover the greater part of the acetone from the percolate by distillation on a water-bath,<sup>8</sup> and, having transferred the residue to a dish, allow the remaining acetone to evaporate spontaneously in a warm place.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

Average dose.—0.030 Gm. = 30 milligrammes ( $\frac{1}{2}$  grain.)

1910

## Oleoresina Zingiberis

## Oleoresin of Ginger

## Oleores. Zingib.

Ginger,<sup>1</sup> in No. 60 powder,<sup>2</sup> *five hundred grammes* ..... 500 Gm. is exhausted.<sup>7</sup> Recover the greater part of the ether from the percolate by distillation, on a water-bath,<sup>8</sup> and, having transferred the residue to a dish, allow the remaining ether to evaporate spontaneously in a warm place.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

Place the ginger in a cylindrical glass percolator, provided with a stop-cock and arranged with cover and a receptacle suitable for volatile liquids.<sup>5</sup> Pack the powder firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted.<sup>7</sup> Recover the greater part of the ether from the percolate by distillation, on a water-bath,<sup>8</sup> and, having transferred the residue to a dish, allow the remaining ether to evaporate spontaneously in a warm place.<sup>9</sup> Keep the oleoresin in a well-stoppered bottle.<sup>10</sup>

Average dose.—Metric, 0.03 Gm.—Apothecaries,  $\frac{1}{2}$  grain.

1) For a description of the different commercial varieties of the official drug, see page 1065 under "Drug used, its collection, preservation, etc."

2) As starch, in the shape of fine granules, constitutes about 20 per cent. of the ginger rhizome, the latter can only be obtained in the form of a uniformly fine powder by reducing the other tissues to a corresponding degree of fineness. It is for this reason and for the purpose of insuring the complete breaking up of all of the small resin cells that the Pharmacopœia directs that the drug be reduced to a No. 60 powder.

3-4) Ether is the solvent which appears to be best adapted to the preparation of this oleoresin in that it completely extracts the pungent principles from the drug and yields a product containing a minimum amount of undesirable extractive matter. According to Garnett and Grier (1909) acetone, which was directed to be used by the Pharmacopœia of 1900, does not completely exhaust ginger, even when a Soxhlet's apparatus is used. It is, therefore, fortunate that the present Pharmacopœia again specifies that ether be used for this purpose.

In the earlier editions of the Pharmacopœia (editions of 1860 and 1870), alcohol was directed to be used as a "follow up" solvent to replace the ether with which percolation was begun. This procedure was abandoned in 1880 for reasons which will be discussed later.

5) Since 1870, the Pharmacopœia has directed that percolation be carried out in a special form of percolater adapted to the use of volatile liquids. For a description of such forms, see Part I under "Apparatus used."

6-7) The method of extracting the drug as outlined in the earlier editions of the Pharmacopœia, the editions of 1860 and 1870, was essentially the same as suggested by Béral in 1834. See Part I, page 929. From a practical standpoint, this method possessed distinct advantages, especially at the time when it was adopted, in that a considerable saving in the cost of the preparation of the oleoresin was effected through the use of alcohol as a "follow up" solvent for replacing the relatively expensive ether. The method, however, was not entirely satisfactory as the finished product contained a considerable amount of undesirable extractive matter owing to the greater solvent properties of the alcohol. Another disadvantage lay

in the fact that a relatively large amount of volatile oil was lost in the removal of the solvent.

The present edition of the Pharmacopœia directs that the drug be completely exhausted by simple percolation with ether. Here, as in the case of the oleoresin of capsicum, the extraction of the drug with the aid of some form of continuous extraction apparatus would effect a considerable saving in solvent and without injury to the finished product.

8-9) With respect to the removal of the solvent from the percolate, the present edition of the Pharmacopœia directs that this be accomplished in greater part by distillation on a water bath and that the remainder be allowed to evaporate spontaneously in a warm place, a procedure similar to that described in the earlier editions. For reasons, identical with those given in the comments on the oleoresin of cubeb (see page 1045), it is thought that the pharmacopœial directions should include specific statements with reference to the amount of solvent to be recovered by distillation and the temperature at which the remainder is to be removed in order to insure greater uniformity in the product obtained.

10) Upon exposure to the air, a portion of the volatile oil contained in the oleoresin is altered (resinified) or lost through evaporation. The preparation should, therefore, be kept in well-stoppered bottles.

### *Yield*

With respect to the solvents, alcohol (95 per cent.), acetone and ether, the yield of oleoresin, in the case of ginger, varies in magnitude in the order in which the solvents are mentioned. For these menstrua, a minimum yield of 2.57 per cent has been reported while the maximum yield has been stated to be as high as 11.1 per cent. When petroleum ether is the solvent used, the yield is much lower, being only about one-half that obtained in the preceding cases. In this connection, the source of the rhizomes is a factor of first importance. Thus, it has been found that Jamaica ginger usually gives the smallest yield and African ginger the highest, while Cochin ginger occupies an intermediate position in this respect. These facts will be brought out more clearly in the tables which follow.

The yield of oleoresin is further influenced by the degree to which the rhizomes have been deprived of the outer corky layer, and, in the case of bleaching, to the manner in which the latter was accomplished. With respect to this statement, the yield, in the case of the unbleached ginger, will be the greatest when decortication is complete. When the rhizomes have been bleached, in addition to being partially or wholly decorticated, the influence of the latter, may be diminished, in part at least, by the process employed in accomplishing the former. Thus, if gypsum or lime have been used for this purpose, the weight of the insoluble material in the rhizomes will be considerably increased, which will have the effect of reducing the percentage yield of oleoresin. These points are also brought out in the tables which follow.

TABLE 63.—*Yield of oleoresin as reported in the literature.*

Date	Observer	Yield of oleoresin to—				Remarks
		Alco- hol	Ace- tone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per cent.	
1834	Béral.....			5.20		
1879	Thresh.....			3.29		Jamaica ginger.
				4.96		Cochin
				3.06		African "
1886	Jones.....	3.58		3.58		
		Alco- hol (sp. gr. 0.82)				
1893	Siggnis.....	5.00				Jamaica ginger, unbleached.
		4.80				bleached (limed)
		6.65				East Indian ginger.
		6.57				
		6.17				African ginger.
		7.00				
1893	Trimble.....			3.97	Benzin 2.48	
1891	Riegel.....	5.00			Benzin 2.50	Jamaica ginger, unbleached.
		8.00		8.00		East Indian ginger, epidermis removed.
1892	Sherrard.....			3.95		
				4.72		
				5.20		
				5.40		
1892	Berlinger.....		5.57			
1893	Dyer and Gilbard			3.00 to 5.20		Upon subsequent extraction with alcohol 0.80 to 1.50 per cent. of material was ob- tained.
1895	Davis.....			4.80 to 4.84		Jamaica ginger.
				5.75 to 6.27		African "
					Methyl alcohol 6.50	
1896	Liverseege.....			5.50		Jamaica ginger.
1897	Glass and Thresh			5.00		Cochin
				4.33		African "
				6.33		
		Alco- hol (90 per cent.)				
1901	Bennet.....	3.94 to		2.57 to		Jamaica ginger, whole.
		5.61		6.41		
		3.41 to		2.97 to		Jamaica ginger, ground.
		5.67		4.60		
		4.91 to				Cochin ginger, whole.
		6.74				
		5.41 to				Cochin ginger, ground.
		6.51				
		5.14 to				African ginger, whole.
		6.61				
		5.14 to				African ginger, ground.
		6.47				
1903	Ballard ...			3.75		Tahiti ginger.
				6.33		Ivory Coast ginger.
		Alco- hol (90 per cent.)		Eth'r (sp. gr. 0.717)		
1903	Southall Bros. & Barclay.....	4.35		4.76		Jamaica ginger.
		4.57		6.04		Cochin
		9.93		11.09		African "

TABLE 63.—*Yield of oleoresin as reported in the literature—Continued.*

Date	Observer	Yield of oleoresin to—				Remarks
		Alco- hol	Ace- tone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per cent Solvent(?)	
1908	Vanderkleed	.....	.....	.....	5.58 5.55	Reported as yield of oleoresin.
1909	Vanderkleed	.....	.....	.....	Solvent(?) 3.14 to 6.91	
1909	Vanderkleed	.....	.....	.....	8.20	Represents the yield from 16 samples of Jamaica ginger. Reported as oleoresin. African ginger.
1909	Vanderkleed	.....	.....	.....	9.03	
1909	Patch	3.70 to 6.20	.....	.....	.....	
1910	Vanderkleed	.....	.....	.....	Solvent(?) 5.63 6.31 10.12	Jamaica ginger. Reported as yield of oleoresin. African ginger. Reported as yield of oleoresin.
1911	Vanderkleed	.....	.....	.....	3.40 to 6.60	
1912	Vanderkleed	.....	.....	.....	7.12 to 9.48	Jamaica ginger. Reported as yield of oleoresin. African ginger. Reported as yield of oleoresin.
1912	Vanderkleed	.....	.....	.....	3.44 to 6.64	
1912	Patch	3.80 to 6.00	.....	.....	6.85 to 11.10	Jamaica ginger. Reported as yield of oleoresin. African ginger. Reported as yield of oleoresin.
1912	Hooper	6.40	.....	.....	.....	
1913	Patch	8.80	.....	.....	.....	Young rhizomes harvested in December.
1913	Patch	4.28	.....	.....	.....	Rhizomes harvested in Feb- ruary.
1913	Vanderkleed	.....	.....	.....	Average yield of 9 samples of ginger.	
1913	Vanderkleed	.....	.....	.....	Solvent(?) 3.10 to 5.75	Reported as yield of oleoresin. Results obtained in extract- ing 37 samples of Jamaica ginger.
1913	Vanderkleed	.....	.....	.....	Solvent(?) 6.85 to 9.92	
1913	Engelhardt	.....	.....	.....	Solvent(?) 2.81 to 5.24	Results obtained in extracting 17 samples of African ginger.
1914	Rippeto	4.98 5.50 6.20 6.23	..... ..... ..... .....	2.79 4.97 5.81 5.45	..... ..... ..... .....	
1914	Vanderkleed	.....	.....	.....	Solvent(?) 5.06	Average yield of 3 samples of Jamaica ginger. Average yield of 3 samples of African ginger.
1915	Vanderkleed	.....	.....	.....	9.00	
		.....	.....	.....	3.93 7.99 8.90	Yield of Jamaica ginger. " " African ginger.

TABLE 64. — *Yield of oleoresin as obtained in the laboratory.*

Yield of oleoresin						Remarks
Date	Observer	Alcohol	Acetone	Ether	Other solvents	
1908	DuMez & Arnold	Per ct. 6.60	Per ct. .....	Per ct. 5.30	Per cent .....	Represents yield using a Soxhlet's extraction app., except in the case of alcohol. <sup>(1)</sup>
1910	DuMez & Netzel	6.33	5.62	5.00	Benzin 2.57	Represents yield using a Soxhlet's extraction app., except in the case of alcohol.
1916	DuMez .....	6.28	5.49	4.92	Petrol. ether 3.15	Represents yield using a Soxhlet's extraction app., except in the case of alcohol.

<sup>1</sup> Jamaica ginger was the variety of the drug used in all cases. When alcohol was the solvent employed, the process of extraction was that of simple percolation.

### *Chemistry of the Drug and Oleoresin.*

#### *Tabulation of Constituents.*

The chemistry of the constituents of ginger is still incomplete in many details, although, it has been the subject of a number of investigations.<sup>1</sup> In the light of our present knowledge, the following may be said to comprise the constituents of importance to the pharmacist: volatile oil, gingerol, resins, fat, wax, gum, sugar, starch and inorganic matter. Thresh<sup>2</sup> has identified the following in the oleoresin prepared by extracting the rhizomes with ether:

Volatile Oil	Resin	Wax
Gingerol	Fat	Ash

#### *Occurrence and Description of Individual Constituents.*

**Volatile Oil.**<sup>3</sup> The volatile oil or so-called essence of ginger is described by Thresh<sup>4</sup> as being a pale straw colored limpid

<sup>1</sup> Morin, Journ. de Pharm. et de Chim. (1823), 9, p. 256; Thresh, Pharm. Journ. (1879), 39, p. 171; Jones, Chem. & Drugg. (1886), 23, p. 413; Gane, Pharm. Journ. (1892), 51, p. 802; Balland, Journ. Pharm. Chim. (1903), 18, p. 248; Reich, Zeitschr. Unters. Nahr. u. Genussm. (1907), 14, p. 549.

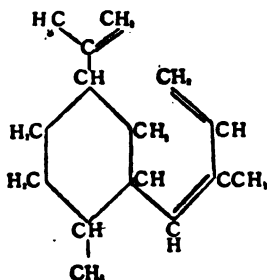
<sup>2</sup> *l. c.*

<sup>3</sup> The description of the volatile oil as given above is for the product obtained from the rhizomes by steam distillation. The oil as it exists in the oleoresin prepared from the rhizomes by extraction with a solvent will undoubtedly differ somewhat.

<sup>4</sup> Pharm. Journ. (1881), 41, p. 198; Year-Book of Pharm. (1881), 18, p. 393.



fluid with a somewhat camphoraceous odor and an aromatic, but not a pungent taste. It is laevogyrate ( $-25$  to  $50^\circ$ ) and has a specific gravity of 0.875 to 0.886. It is soluble in strong alcohol, petroleum ether, carbon disulphide, benzene, turpentine and glacial acetic acid. The principal constituent of the oil, a sesquiterpene, gingerene or zingiberene, ( $C_{15}H_{24}$ ) was first definitely described by von Soden and Rojahn<sup>5</sup> in 1900. According to Semmler and Becker,<sup>6</sup> it is a monocyclic butadiene having the following structure:



The former investigators also identified d-camphene and phellandrene<sup>7</sup> in the lower boiling fractions. In addition to these hydrocarbons, Schimmel & Company<sup>8</sup> have reported the presence of citral, cineol, borneol and probably geraniol, and Dodge<sup>9</sup> the presence of an aldehyde of the probable formula,  $n-C_9H_{19}CHO$ .

The volatile oil has been found to be present in the rhizomes in varying quantities depending on their age before harvesting, the methods of curing and their geographical source.<sup>10</sup> Ac-

<sup>5</sup> Pharm. Ztg. (1900), 45, p. 414.

<sup>6</sup> Ber. d. deutsch. chem. Gesell. (1913), 46, p. 1814.

<sup>7</sup> Schimmel & Co. Semi-Ann. Rep. (1905), II, p. 38.

<sup>8</sup> Phellandrene and d-camphene were identified in the oil by Bertram and Walbaum in 1894. Journ. f. prakt. Chem. (1894), 49, p. 18.

<sup>9</sup> Chem. Abs. (1912), 6, 3, p. 2976; Orig. Com. 8th Intern. Congr. Appl. Chem. 6 p. 77.

<sup>10</sup> Gane reports the presence of volatile oil in ginger as follows: Jamaica 0.64 per cent., Cochin 1.35 per cent., African 1.615 per cent., Fijian 1.45 per cent. Pharm. Journ. (1892), 51, p. 802.

Thresh obtained 0.75 per cent. of oil from Jamaica ginger, 1.35 per cent. from Cochin and 1.61 per cent. from African. Pharm. Journ. (1879), 39, p. 1. 191.

Haensel states that he obtained only 1.072 per cent. of volatile oil from Jamaica ginger, whereas other sorts yielded from 2 to 3 per cent. Pharm. Ztg. (1903), 48, p. 58.

Bennet found 0.20 to 0.90 per cent. of oil in Jamaica ginger, Pharm. Journ. (1901), 66, p. 522.

Reich gives the following as the volatile oil content of various sorts of

according to Cripps and Brown a "good ginger" will yield from 2.24 to 3.48 per cent.<sup>11</sup>

*Gingerol.* Gingerol or zingiberol<sup>12</sup> is the constituent or mixture of constituents to which ginger is said to owe its pungency. It is a colorless, odorless, viscid fluid possessing an extreme pungency. Its exact composition has not been determined, the most recent investigations indicating that it is a mixture of phenols.<sup>13</sup> It is readily soluble in strong alcohol, carbon disulphide, benzol and oil of turpentine, but only slightly soluble in petroleum ether.

Gingerol is present in the rhizomes in amounts varying from 0.6 to 1.82 per cent.<sup>14</sup>

*Resins.* The resins of ginger have been isolated and described by Thresh.<sup>15</sup> This investigator recognizes four individuals with respect to their physical properties and their behavior toward acids and alkalies, viz: a neutral resin, an  $\alpha$ -resin, a  $\beta$ -resin and a  $\gamma$ -resin.

The neutral resin is stated to be a black, pitch-like substance soluble in ether, alcohol, benzene and oil of turpentine, but insoluble in petroleum ether and carbon disulphide.

The  $\alpha$ -resin is a soft, but brittle substance soluble in ether and alcohol, but insoluble in the remainder of the above mentioned solvents.

The  $\beta$ -resin is also soft and brittle, but is soluble in all of the above solvents.

The  $\gamma$ -resin is firmer in consistence and is soluble in ether, alcohol and petroleum ether.

The total resin content of the rhizomes varies to a considerable

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ginger: Cochin 1.38 per cent., Japan 1.38 per cent., Bengal 1.6 per cent., African 2.54 per cent. Zeitschr. Unters. Nahr. u. Genussm. (1907), 14, p. 549.

<sup>11</sup> Analyst (1909), 34, p. 519.

<sup>12</sup> The term *gingerol* was first used by Thresh in 1884 to designate the pungent principle of ginger. Year-Book of Pharm. (1884), 21, p. 516.

*Zingiberol* is evidently a modification of the above, the idea being to bring the nomenclature in closer conformity with the name of the botanical source—*Zingiberis officinale* Roscoe.

<sup>13</sup> Garnet and Grier, Year-Book of Pharm. (1907), 44, p. 441.

<sup>14</sup> Thresh obtained gingerol in the following quantities: Jamaica ginger 0.66 per cent., Cochin 0.60 per cent., African 1.45 per cent. Pharm. Journ. (1879), 39, p. 193.

Gane reports the presence of the following percentages: Jamaica 0.84 per cent., Cochin 0.60 per cent., African 1.45 per cent., Fijian 1.82 per cent. Pharm. Journ. (1892), 51, p. 802.

<sup>15</sup> Pharm. Journ. (1879), 39, p. 193.

extent and appears to depend principally on their geographical source. The minimum yield (1.18 per cent.) has been obtained from Jamaica ginger, the maximum yield (4.47 per cent.) from the Fijian rhizome.<sup>16</sup>

*Fat and Wax.* Little or no work has been done toward determining the composition of the fat or wax in ginger. The two substances, combined, are stated to constitute 0.70 to 1.225 per cent. of the rhizome.<sup>17</sup>

*Ash.* The qualitative examination of the ash of ginger has been undertaken by Thresh,<sup>18</sup> who reports the presence of the basic elements: K, Ca, Mg, Mn,<sup>19</sup> and Fe combined with  $H_2CO_3$  and  $H_3PO_4$ . The ash of African ginger is stated to contain the largest amount of manganese.

The ash content<sup>20</sup> of the whole rhizome appears to be influenced but little by the locality from which obtained, 3.0 to 5.5 per cent. being conservative limits for the usual commercial varieties. Peeling<sup>21</sup> appears to decrease the amount of ash while bleaching<sup>22</sup> (liming) increases it.

### *Constituents of Therapeutic Importance.*

The physiological action of the oleoresin of ginger was at one time thought to be due to the resin content, but the work of Thresh<sup>1</sup> has shown the pungency to be the property of the phenolic constituents known collectively as gingerol. The car-

<sup>16</sup> Thresh reports the total resin content of ginger as follows: Jamaica 1.18 per cent., Cochín 1.815 per cent., African 3.775 per cent., *Pharm. Journ.* (1879), 39, p. 173.

Gane noted the presence of the following percentages: Jamaica ginger 1.76 per cent., Cochín 1.815 per cent., African 3.775 per cent., Fijian 4.475 per cent. *Pharm. Journ.* (1892), 51, p. 802.

<sup>17</sup> The combined fat and wax present in ginger is stated by Thresh to be as follows: Jamaica 0.70 per cent., Cochín 1.205 per cent., African 1.225 per cent. *l. c.*

Gane found the following amounts: Jamaica ginger 0.92 per cent., Cochín 1.20 per cent., African 1.225 per cent., Bengal 0.86 per cent., *L. C.*

<sup>18</sup> *Pharm. Journ.* (1879), 29 pp. 174 and 193.

<sup>19</sup> See also Flueckiger, *Ibid.* (1872), 32, p. 208.

<sup>20</sup> C. Richardson. *Bull.* 13, Dept. Agr. Washington, 1887; Gane, *Pharm. Journ.* (1892), 51, p. 802; Liverseege, *Vierteljahresschr. Nahrungs- u. Genussm.* (1896), 11, p. 353; Glass, *Pharm. Journ.* (1897), 53, p. 245; Bennet, *Ibid.* (1901), 66, p. 522.

<sup>21</sup> Winton, Ogden and Mitchell obtained 3.66 to 4.06 per cent. of ash for unpeeled and unbleached Cochín ginger, 3.36 per cent. for the same when peeled and bleached. *Rep. Conn. Agr. Exp. Sta.* (1898), p. 202; (1899), p. 102.

<sup>22</sup> Davis reports 5.20 per cent. of ash for unbleached Jamaica ginger, 6.55 per cent. for the bleached. *Pharm. Journ.* (1895), 54, p. 472.

<sup>1</sup> *Year-Book of Pharm.* (1884), 21, p. 516.

minative action of the preparation must also be attributed in part to the volatile oil contained therein.

### *Physical Properties.*

**Color:** The oleoresins examined in the laboratory were observed to be rather dark brown in color when spread out in thin layers on a white porcelain surface. This property, however, is reported to vary somewhat with the variety and condition of the ginger used in making the preparation. When African ginger is employed, the oleoresin is stated to be dark brown in color, whereas, uncoated Jamaica ginger is said to yield a preparation comparatively light in color.<sup>1</sup>

**Odor:** The oleoresin, when prepared according to the official process, has the full aroma of ginger, the quality of which is stated to be influenced largely by the variety of ginger used.<sup>2</sup>

**Taste:** The preparation has the sharp pungency and flavor of ginger. This property, like the odor, is stated to vary with the variety of ginger used, Jamaica ginger yielding the product with the best flavor.<sup>3</sup>

**Consistence:** The oleoresin is a thick liquid, being of about the consistence of molasses, as a rule, but varying somewhat with the variety of the ginger used in its preparation. The fluidity is said to be the greatest when prepared from Jamaica ginger and the least when made from the African variety.<sup>4</sup>

**Solubility:** The oleoresin is soluble in absolute alcohol, acetone, ether, chloroform, and glacial acetic acid. It is partially soluble in petroleum ether, the extent of its solubility depending on the solvent used in its preparation as is shown in the following table:

TABLE 65—*Solubility of the oleoresin in petroleum ether.*

Solvent used in preparing the oleoresin.	Alcohol	Acetone	Ether
Per cent. of oleoresin soluble in petrol. ether..	45.55	49.59	69.44

<sup>1</sup> Parrish, *Treatise on Pharmacy*, (1867), p. 233.

<sup>2</sup> Idris (1898).

<sup>3</sup> Idris (1898).

<sup>4</sup> Idris (1898).

As will be noticed this difference in solubility is quite pronounced and it should, therefore, serve as a ready means of identifying the solvent used in the manufacture of the preparation.

*Specific gravity:* At 25°C a specific gravity of 1.020 to 1.036 was found for this oleoresin when acetone or ether were employed in its preparation. This constant was observed to be slightly higher when alcohol was used as a menstruum and considerably lower (less than 1.000) when petroleum ether was employed. In the case of the commercial samples examined, a low specific gravity is to be attributed to the presence of unevaporated solvent in one instance, and in the other, it is thought to be due to an abnormally large volatile oil content. The data obtained in the examination of laboratory and commercial samples are given in the tables which follow.

TABLE 66—*Specific gravities of oleoresins prepared in the laboratory,*

Sample No.	Date	Observer	Solvent	Specific gravity <sup>1</sup>
1.....	1916	DuMez.....	Alcohol.....	At 25° C 1.041
2.....	"	" .....	Acetone.....	1.030
3.....	"	" .....	" .....	1.033
4.....	"	" .....	" .....	1.036
5.....	"	" .....	Ether.....	1.020
6.....	"	" .....	Petrol. ether.....	0.990

TABLE 67—*Specific gravities of commercial oleoresins.*

Sample No.	Date	Observer	Source	Specific gravity
1.....	1916	DuMez.....	Squibb & Sons.....	At 25° C 0.997 <sup>1</sup>
2.....	"	" .....	Sharp & Dohme.....	1.014
3.....	"	" .....	Lilly & Co.....	1.024

<sup>1</sup> Contained ether.

*Refractive index:* A refractive index of about 1.517 at 25°C was observed for the preparations made in the laboratory with acetone or ether. When alcohol was employed in extracting the drug, the resulting product was found to have a slightly higher refractive index, while petroleum ether yielded an oleoresin in

which this constant was observed to be considerably lower. The low refractive index found for two of the commercial samples was very likely due to the fact that they contained twice as much volatile matter (principally essential oil) as the laboratory preparations. The effect of this influence, together with that produced by the presence of unevaporated solvent, is brought out in the following tables:

TABLE 68.—*Refractive indices of the oleoresins prepared in laboratory.*

Sample No.	Date	Observer	Solvent	Refractive index
1.....	1916	DuMez .....	Alcohol .....	At 25° C 1.520
2.....	"	" .....	Acetone.....	1.517
3.....	"	" .....	" .....	1.517
4.....	"	" .....	" .....	1.518
5.....	"	" .....	Ether .....	1.517
6.....	"	" .....	Petrol. ether.....	1.501

TABLE 69.—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
1.....	1916	DuMez .....	Squibb & Sons.....	At 25° C 1.501 <sup>1</sup>
2.....	"	" .....	Sharp & Dohme.....	1.505
2.....	"	" .....	Lilly & Co .....	1.512

<sup>1</sup> Contained ether.

### *Chemical Properties.*

*Loss in weight on heating:* The oleoresins prepared in the laboratory lost, as a rule, between 11 and 13 per cent. of their weight on heating at 110°C, whereas the loss in the case of the commercial samples was about twice as great. While this difference may have been due to the employment of different methods in the making of these preparations (a vacuum pan having probably been used in the removal of the solvent in the case of the commercial products), it is more likely the result of the presence of a greater amount of volatile oil in the drugs from which the latter were prepared. The loss in weight

as found for the preparations examined in the laboratory is given in the tables which follow.

TABLE 70.—*Laboratory preparations—loss in weight on heating.*

Sample No.	Date.	Observer.	Solvent.	Per ct. of loss on heating.
1.....	1916	DuMez.....	Alcohol.....	At 110° C 12.82
2.....	"	".....	Acetone.....	11.92
5.....	"	".....	".....	7.34
6.....	"	".....	".....	11.54
3.....	"	".....	Ether.....	11.08
4.....	"	".....	Petrol. ether.....	11.50

TABLE 80.—*Commercial samples—loss in weight on heating.*

Sample No.	Date	Observer	Source	Per cent of loss on heating
1.....	1916	DuMez.....	Lilly & Co.....	At 110° C 18.90
2.....	"	".....	Squibb & Sons.....	21.39 <sup>1</sup>
3.....	"	".....	Sharp & Dohme.....	22.97

<sup>1</sup> The presence of ether could be detected by the odor.

**Ash content:** The ash content of the oleoresin prepared with acetone was found to be 0.28 per cent., whereas, that of the preparation made with ether was only 0.14 per cent. The values obtained for the commercial samples examined also showed this variation due to the nature of the solvent. Copper, although detected in two of these preparations (commercial oleoresins), was present in such small quantities that the results were not affected materially thereby. The following tables show the results obtained in the ash determinations made in the laboratory.

TABLE 81.—*Ash contents of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Per cent of ash
1.....	1916	DuMez.....	Alcohol.....	0.42
2.....	"	".....	Acetone.....	0.50
3.....	"	".....	".....	0.26
4.....	"	".....	".....	0.28
5.....	"	".....	Ether.....	0.14
6.....	"	".....	Petrol. ether.....	0.06

TABLE 82.—*Ash contents of commercial oleoresins.*

Sample No.	Date	Observer	Source	Per cent of ash	Foreign constituents
1.....	1916	DuMez .....	Squibb & Sons.....	0.15 <sup>1</sup>	Copper
2.....	"	" .....	Lilly & Co .....	0.26	
3.....	"	" .....	Sharp & Dohme.....	0.27	

<sup>1</sup> Contained ether.

*Acid number:* The acid numbers obtained for the oleoresins prepared in the laboratory were found to be fairly uniform regardless of the solvent employed in extracting the drug, except in the case of petroleum ether, when the value found was low, namely, 11.2. The values obtained for the commercial samples examined were almost identical with those obtained for the laboratory preparations, even though the former in all cases contained about twice as much volatile matter (generally essential oil, in one case, unevaporated solvent in addition) as the latter. The values obtained for this constant in the laboratory are given in the tables which follow.

TABLE 83—*Acid numbers of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Acid number
1.....	1916	DuMez.....	Alcohol.....	18.9
2.....	"	" .....	Acetone .....	14.5
3.....	"	" .....	" .....	18.8
4.....	"	" .....	" .....	18.5
5.....	"	" .....	Ether .....	18.7
6.....	"	" .....	Petrol. ether .....	11.2

TABLE 84—*Acid numbers of commercial oleoresins.*

Sample No.	Date	Observer	Source	Acid number
1.....	1916	DuMez.....	Lilly & Co.....	18.8
2.....	"	" .....	Squibb & Sons.....	18.8 <sup>1</sup>
3.....	"	" .....	Sharp & Dohme.....	14.0

<sup>1</sup> Contained ether.

*Saponification value:* Saponification values of 103.4 to 110.4 were obtained for the oleoresin when prepared with



acetone. For the preparation in which ether was employed as a menstruum in extracting the drug, a saponification value of 102.9 was obtained. The comparatively low values obtained for the commercial samples examined are to be accounted for by the fact that in all cases, they contained nearly twice as much volatile matter (presumably essential oil) as the laboratory preparations. The values found for this constant are given in the tables which follow.

TABLE 85—*Saponification values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Saponification value
1.....	1916	DuMez.....	Alcohol.....	119.4
2.....	"	".....	Acetone.....	103.4
3.....	"	".....	".....	110.4
4.....	"	".....	".....	105.7
5.....	"	".....	Ether.....	102.9
6.....	"	".....	Petrol. ether.....	78.1

TABLE 86—*Saponification values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Saponification value
1.....	1916	DuMez.....	Sharp & Dohme.....	94.1
2.....	"	".....	Squibb & Sons.....	98.4 <sup>1</sup>
3.....	"	".....	Lilly & Co.....	89.9

<sup>1</sup> Contained a trace of ether.

*Iodine value:* Iodine values of 122.4 to 124.1 were obtained for the oleoresin when prepared with acetone. The preparations made with alcohol or ether gave values very near the same, whereas, the value of this constant was somewhat higher (126.9) when petroleum ether was the solvent employed. With respect to the commercial samples, the values found were lower in all cases. In one instance, this was due to the presence of unevaporated solvent, while, in the other cases it is to be attributed to the relatively large amount of volatile matter (essential oil) present. The iodine values found for the preparations examined in the laboratory follow.

TABLE 87.—*Iodine values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Iodine value
1.....	1916	DuMez .....	Alcohol .....	122.3
2.....	"	" .....	Acetone .....	122.4
3.....	"	" .....	" .....	111.5 <sup>1</sup>
4.....	"	" .....	" .....	124.1
5.....	"	" .....	Ether .....	121.1
6.....	"	" .....	Petrol. ether.....	126.9

<sup>1</sup> The drug in this instance was extracted by simple percolation.

TABLE 88.—*Iodine values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Iodine value
1.....	1916	DuMez .....	Scribb & Sons .....	104.2 <sup>1</sup>
2.....	"	" .....	Lilly & Co. ....	108.9
3.....	"	" .....	Sharp & Dohme ..	112.0

<sup>1</sup> Contained ether.

### *Special Qualitative Tests.*

Most of the qualitative methods which have been mentioned in connection with the standardization of this preparation are of the nature of tests for the detection of adulterations. The oleoresin of capsicum<sup>1</sup> is the adulterant which appears to have received special attention, several methods for detecting its presence having been reported.

#### *Tests for the Presence of the Oleoresin of Capsicum*

La Wall, in 1910, pointed out the necessity of a test for the presence of the oleoresin of capsicum as he had observed that many of the commercial samples of the oleoresin of ginger used in the preparation of ginger ale extracts were adulterated with this substance. At the same time, he also described a method whereby this form of adulteration might be detected. His method is almost identical with that of Garnett and Grier published in 1907, both being based on the destruction of the

<sup>1</sup> While the oleoresin of capsicum *per se* may occasionally be added to the finished product, it is thought that the adulteration is usually accomplished by mixing capsicum with the ginger previous to the extraction of the oleoresin.

pungent principles (gingerol) of the oleoresin of ginger with alkalis, whereby the pungent principle (capsicin) of the oleoresin of capsicum remains unaltered. As it was subsequently found that the pungent principles of the former were not completely destroyed by this treatment, Nelson proposed a modification of the above methods, in which he makes use of manganese dioxide for completing the disintegration of these constituents. Full descriptions of these methods follow:

*Method of Garnett and Grier (1907):* Digest 1 gram of the oleoresin for 15 minutes on a water bath with a small quantity of caustic alkali dissolved in alcohol. Evaporate the solution to remove the alcohol and make the residue faintly acid with hydrochloric acid. Transfer the liquid to a test tube and shake it with 5 cubic centimeters of ether which have previously been used to rinse the dish. Allow the mixture to stand quietly and then taste the separated ethereal layer. If sharply pungent, adulteration with capsicum is indicated.

*Method of La Wall (1910):* Add 10 cubic centimeters of half-normal alcoholic potassium hydroxide solution to 1 gram of the oleoresin contained in a shallow porcelain dish and evaporate to dryness on a water bath. Dissolve the residue in 50 cubic centimeters of water and transfer the solution to a separatory funnel. Add 20 cubic centimeters of ether and shake vigorously. After allowing the mixture to stand until the ether has separated, run the latter off on a watch glass and expose it until the solvent has all evaporated. The residue should have a warm camphoraceous taste. A sharp pungent taste indicates adulteration with capsicum.

*Method of Nelson (1902):*<sup>2</sup> Add 10 cubic centimeters of double-normal alcoholic potassium hydroxide solution to one gram of the oleoresin contained in a porcelain dish and evaporate on a steam bath. Add about 0.1 gram of powdered manganese dioxide and 5 to 10 cubic centimeters of water, and continue heating for about 20 minutes, or until all of the volatile oil has been expelled. Cool, acidify with dilute sulphuric acid and extract at once with petroleum ether. Evaporate the petroleum ether solution in a small crucible, keeping the residue within as small an area as possible. When all of the solvent has evaporated, apply the tongue to the residue, being careful to keep the material on the tip. If capsicum is present, the characteristic burning sensation will soon be felt.

The latter is the method which was employed in making the test in the laboratory. In no case, however, was capsicum detected in the samples examined.

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<sup>2</sup> Journ. Indust. and Eng. Chem. (1910), 2, p. 419.

*Special Quantitative Tests.*

While the matter of determining the quality of the unadulterated product has apparently received but little attention, two distinct methods have, nevertheless, been made use of in its evaluation. They are the methods of Garnett and Grier for the determination of the gingerol content, and the physiological test employed by the H. K. Mulford Company.

*Methods for the Estimation of the Gingerol Content.*

The only method of an analytical nature which has been suggested for the quantitative evaluation of this oleoresin is based on the fact that the pungent principles, gingerol, are more readily soluble in 60 per cent alcohol, than in petroleum ether. A description of the manner in which this assay is carried out follows.

*Method of Garnett and Grier (1909):* Dissolve the gingerol by boiling about 1 gram of the oleoresin with several portions of petroleum ether, filter the solutions thus obtained and remove the solvent by evaporation on a water bath. Dissolve the residue in alcohol (60 per cent.) added in three separate portions, shake the united alcoholic solutions with a small amount of petroleum ether to remove traces of fat and remove the alcohol from the hydro-alcoholic portion by evaporation. Shake the residual liquid with 3 portions of ether added successively, filter the combined shakings into a tared flask, remove the ether by evaporation on a water bath, dry at 100°C and weigh. In the final shaking out, carbon disulphide or chloroform may be used in place of the ether.

The use of this method in the laboratory has shown that it gives fairly constant results, and, as it is easily carried out, it should prove to be of practical value. The results obtained in the examination of oleoresins prepared in the laboratory and those obtained from commercial sources are given in the following tables:

TABLE 89—*Gingerol content of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Gingerol content
1.....	1916	DuMez.....	Alcohol.....	Per cent. 27.2
2.....	"	"	Acetone.....	28.2
3.....	"	"	Ether.....	27.5
4.....	"	"	Petrol. ether.....	43.9

TABLE 90—*Gingerol content of commercial oleoresins.*

Sample No.	Date	Observer	Source	Gingerol content
				Per cent.
1.....	1916	DuMez.....	Lilly & Co.....	19.5
2.....	"	".....	Sharp & Dobme.....	24.0
3.....	"	".....	Squibb & Sons.....	28.2

The first of the preceding tables shows that the gingerol content varies with the solvent employed in the preparation of the oleoresin. Further, that this variation is not in inverse ratio to the yield of oleoresin obtained as might be expected, but is exceptionally low in the case of acetone due to the fact that it is a difficult matter to completely exhaust the drug when the latter is the solvent used.

The low gingerol content of two of the commercial samples as shown in the second table, points to the use of acetone in their preparation. A similar effect might, however, be produced when ether or alcohol are employed if the ginger used is of poor quality (low in gingerol content,) or if percolation is terminated before complete exhaustion of the drug has taken place. The oleoresin obtained from Squibb and Sons is stated to have been prepared with ether, which statement is confirmed by the result obtained in the determination of the gingerol content as is also shown in the second table.

### *Physiological Tests.*

The H. K. Mulford Company reports the use of a physiological test for determining the quality of this oleoresin. As an arbitrary standard, the firm has taken a preparation which is pungent to the taste in a maximum dilution of 1 to 20,000. While there is no information at hand to indicate what solvent was employed as the diluent, experience in the laboratory has shown that dilute alcohol (50 per cent.) may be used for this purpose. After vigorously shaking the oleoresin with alcohol, the resulting solution should preferably be filtered before applying to the tongue. Although no extensive series of experiments were made with this test in the laboratory, the results obtained would appear to indicate that the above standard is rather low as the pungency in the preparations examined was

easily perceptible in dilutions of 1 to 30,000. In view of the fact that personal idiosyncrasy must be a factor in applying this test, the use of the previously described method for the estimation of the gingerol content is thought to be more preferable for use in this connection.

### *Adulterations*

There is no evidence to show that the oleoresin as prepared for pharmaceutical use is adulterated. La Wall,<sup>1</sup> however, states that the commercial article used in the manufacture of ginger ale frequently contains oleoresin of capsicum.

A trace of copper was found in most of the commercial samples examined. See under "Ash content."

### OLEORESIN OF LUPULIN

#### *Synonyms*

*Aetherisches Lupulineextrakt*, Nat. Disp. 1879.

*Extractum Lupulini*, Hirsh, Univ. P. 1902, No. 1222.

*Extractum Lupulini aethereum*, Nat. Disp. 1879.

*Oleoresina Lupulinae*, U. S. P. 1860.

*Oleoresina Lupulini*, U. S. P. 1880.

*Oléorésine de Lupuline*, U. S. Disp. 1907.

*Ethereal Extract of Lupulin*, King's Am. Disp. (1900), p. 1333.

#### *History*

The first mention of the oleoresin of lupulin which could be found in pharmaceutical literature appeared in Procter's article, "Formulae for fluid extracts in reference to their more general adoption in the next Pharmacopœia," published in 1859. Procter's oleoresin was in reality an ethereal extract, ether having been the menstruum employed in exhausting the drug. In this connection, it is interesting to note that the extract prepared with the use of alcohol had previously been brought to the notice of the American pharmacist by Livermore in 1853, while the attention of the European pharmacist had been directed to the same by Planche as early as 1823. The oleoresin was first admitted to the *United States Pharmacopœia* in 1860, in which it remained official for more than half a century, having been

<sup>1</sup> LaWall (1910).

omitted from the present revised edition. It has never received recognition by any of the foreign pharmacopœias.

*Drug Used, Its Collection, Preservation, Etc.*

Lupulin has not been included in the late edition of the *United States Pharmacopœia*. In the preceding edition, it was defined as "the glandular trichomes separated from the fruit of *Humulus Lupulus* Linné (Fam. *Moraceae*)."

The drug, as it occurs on the market, is of varying degrees of purity due, principally, to the method of obtaining it. While some of it is probably obtained by picking the scales from the fruits and then shaking or rubbing the glands through a fine sieve, the bulk of the commercial article consists of the sweepings gathered up from the floors of the hop bins.<sup>1</sup> Such being the case, it is only natural to expect contamination with sand and other earthy materials. The impurities, in part, are usually removed by washing with water when the sand settles to the bottom and the lupulin is skimmed off and dried.

The glands, on storing, especially if exposed to the air, undergo a change, becoming dark brown in color and developing a rancid odor. Rabak<sup>2</sup> and Russell,<sup>3</sup> respectively, have shown one of the changes to be a conversion of the so-called soft resin into the hard. The development of the disagreeable odor has been attributed to the formation of valeric acid<sup>4</sup> resulting from the oxidation of one or more of the constituents. In view of the foregoing, the *British Pharmacopœia* directs that the drug be renewed annually and rejected as soon as it becomes dark in color or develops a cheesy odor.

In this connection, it should also be stated that hops are often sulphured previous to storing. To what extent, if any, this treatment affects the quality of the lupulin obtained therefrom and later the oleoresin, does not appear to have been determined.

<sup>1</sup> Flueckiger, *Pharmakognose des Pflanzenreichs* (1891), p. 255.

<sup>2</sup> Bull. No. 271, U. S. Dept. of Agric. (1913), p. 13.

<sup>3</sup> Bull. No. 282, U. S. Dept. of Agric. (1915), p. 9.

<sup>4</sup> Bungener, *Pharm. Journ.* (1884), 43, p. 1008.

*U. S. P. Text and Comments Thereon.*

The oleoresin, which was official in the *United States Pharmacopæia* from 1860 to 1900, has been omitted from the last edition (edition of 1910).

1864

## Oleoresina Lupulinae

## Oleoresin of Lupulin

Take of Lupulin<sup>1</sup> twelve troyounces; distillation on a water-bath, eighteen  
Ether<sup>2</sup> a sufficient quantity. fluidounces of ether,<sup>3</sup> and expose the

Put the lupulin into a narrow cylindrical percolator, press it firmly, and residue, in a capsule, until the remaining ether has evaporated.<sup>6</sup> Lastly, gradually pour ether upon it until keep the oleoresin in a wide-mouthed thirty fluidounces of filtered liquid bottle, well stopped.<sup>7</sup>  
have passed.<sup>4</sup> Recover from this, by

1870

## Oleoresina Lupulinae

## Oleoresin of Lupulin

Take of Lupulin<sup>1</sup> twelve troyounces; ounces of liquid have slowly passed.<sup>4</sup>  
Ether<sup>2</sup> a sufficient quantity. Recover the greater part of the ether

Put the lupulin into a narrow cylindrical percolator, provided with a by distillation on a water-bath,<sup>5</sup> and expose the residue in a capsule, until stop-cock, and arranged with cover the remaining ether has evaporated.<sup>6</sup> Lastly, keep the oleoresin in a wide-liquids,<sup>7</sup> press it firmly, and gradually mouthed bottle, well stopped.<sup>7</sup>  
pour ether upon it, until twenty fluid-

1880

## Oleoresina Lupulini

## Oleoresin of Lupulin

[Oleoresina Lupulinae, Pharm., 1870]

Lupulin,<sup>1</sup> one hundred parts ....100. parts of liquid have slowly passed.<sup>4</sup>  
Stronger Ether<sup>2</sup>, a sufficient quantity. Recover the greater part of the ether

Put the lupulin into a narrow cylindrical percolator, provided with a by distillation on a water-bath,<sup>5</sup> and expose the residue, in a capsule, until cover and receptacle suitable for the remaining ether has evaporated.<sup>6</sup> Keep the oleoresin in a well-stopped, wide-mouthed bottle.<sup>7</sup>  
gradually pour stronger ether upon it, until one hundred and fifty (150)



1890

## Oleoresina Lupulini

## Oleoresin of Lupulin

Lupulin,<sup>1</sup> *one hundred grammes*..... the drug is exhausted.<sup>4</sup> Recover the  
 ..... 100 Gm. greater part of the ether from the  
 Ether,<sup>2</sup> *a sufficient quantity.* percolate by distillation on a water-

Put the lupulin into a cylindrical bath,<sup>3</sup> and, having transferred the  
 glass percolator, provided with a residue to a capsule, allow the re-  
 stop-cock, and arranged with a cover maining ether to evaporate spontan-  
 and receptacle suitable for volatile eously.<sup>4</sup>  
 liquids.<sup>2</sup> Press the drug very lightly, Keep the product in a well-stop-  
 and percolate slowly with ether, pered bottle,<sup>4</sup>  
 added in successive portions, until

1900

## Oleoresina Lupulini

## Oleoresin of Lupulin

Lupulin,<sup>1</sup> *five hundred grammes*..... Recover the greater part of the ace-  
 ..... 500 Gm. tone from the percolate by distilla-  
 Acetone,<sup>2</sup> *a sufficient quantity.* tion on a water-bath,<sup>3</sup> and, having

Introduce the lupulin into a cylin- transferred the residue to a dish, al-  
 drical glass percolator, provided with low the remaining acetone to evap-  
 a stop-cock, and arranged with a orate spontaneously in a warm place.<sup>4</sup>  
 cover and a receptacle suitable for Keep the oleoresin in a well-stoppered  
 volatile liquids.<sup>2</sup> Press the powder bottle.<sup>4</sup>  
 very lightly, and percolate slowly Average dose.—0.200 = Gm. 200  
 with acetone, added in successive milligrammes (3 grains).  
 tions, until the lupulin is exhausted.<sup>4</sup>

1) For description of the drug, see page 1088 under "Drug used, its collection, preservation, etc."

2) The solvents which have been used for the purpose of extracting lupulin are ether, acetone and alcohol. Of these, the first two have been recognized at different times by the Pharmacopœia, acetone being the solvent which was directed to be used by the edition of 1900, whereas ether was specified in previous editions.

With respect to the relative values of the above, from a therapeutical standpoint, a statement cannot be made owing to the lack of specific information on the subject. From a pharmaceutical standpoint, however, ether and acetone, re-

spectively possess an advantage over alcohol in that they extract less inert material and yield products which are softer in consistence and conform more closely in their general properties to the other members of this class of preparations. The products obtained, even when using acetone or ether, are, however, more of the nature of an extract than an oleoresin.

A better solvent for use in this connection would appear to be petroleum ether. While, it has apparently never received consideration for this purpose, it appears to be particularly well adapted to the same in that it completely extracts the valuable constituents of the drug (see soft resins, page 1095) with but little of the inert material and yields a product of such consistence that it can be poured.

3) For a description of the various forms of percolation conforming to the pharmacopœial specifications for use in this connection, see Part I under "Apparatus used."

4) The various editions of the Pharmacopœia in which this preparation has been official have directed that the material composing the oleoresin be extracted from the drug by simple percolation. In the earlier editions, percolation was directed to be continued until a certain definite amount of percolate was obtained, whereas, the pharmacopœias of 1890 and 1900 required that the operation be continued until the drug was exhausted. In either case, the quantity of solvent required is considerably greater than that which is necessary to completely exhaust the drug when some form of continuous extractor is used. Since the quality of the finished product is the same in both cases, it is thought that the later method of extraction is to be preferred.

5-6) Owing to the fact that certain constituents of the oleoresin are prone to undergo changes when the latter is exposed to the air (see page 1088 under "Drug used, its collection, preservation, etc."), the pharmacopœial directions, that the last portions be allowed to evaporate spontaneously, are unfortunate. It is thought that a better procedure would be to evaporate the solvent completely at the temperature of the water bath, thereby considerably shortening the time of exposure.

8) For the reasons just mentioned, the finished product should be kept in well-stoppered bottles.

*Yield*

The yield of oleoresin to ether is usually given in the text-books and treatises on pharmacy as 50 to 60 per cent., while a yield of 32.49 to 70.8 per cent. has been reported in the journals. The irregularity in the quality of the lupulin as ordinarily found on the market very likely accounts for this variation. The drug, when of good quality should give a yield of at least 60 per cent. The following tables show the variation in the yield as reported in the literature, also, the results obtained in the laboratory.

TABLE 91—Yield of oleoresin as reported in the literature.

Date	Observer	Yield of oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per ct.	
1853	Livermore.....	66.00	.....	.....	.....	
1888	Trimble.....	.....	.....	60.59	} Benzin 7.04	
1892	Beringer.....	.....	71.00	70.80		
1892	Sherrard.....	.....	.....	86.50	.....	
1907	Van der Harst ..	.....	.....	52.00	.....	
		.....	.....	65.00	.....	
1906	Dohme and Engelhardt.....	.....	.....	56.00	.....	
1909	Parson.....	.....	.....	54.00	.....	
		.....	.....	60.10	.....	
		.....	.....	66.70	.....	
1909	Bernegau.....	.....	.....	34.00 to 65.80	.....	Results obtained in the extraction of 10 samples of lupulin.
1909	Dohme & Engelhardt.....	.....	.....	47.00	.....	
		.....	.....	50.00	.....	
		.....	.....	53.00	.....	
1911	Bernegau.....	.....	.....	57.70	.....	
		.....	.....	58.90	.....	
1911	Francis.....	.....	.....	62.10	.....	Seven of 8 samples yielded more than 60 per cent. of extractive to ether.
		.....	.....	60.0+	.....	
1913	Gane.....	.....	.....	44.94 to 65.60	.....	Results obtained in the extraction of 4 samples of lupulin.
1913	Patch.....	.....	.....	63.96 to 77.82	.....	
1913	Engelhardt.....	.....	.....	Below 60.00	.....	Results obtained in the extraction of 53 samples of lupulin. Eight of 12 samples of lupulin extracted gave below 60 per cent. of ether soluble matter.
1914	Rippetoe.....	.....	.....	32.49	.....	
		.....	.....	55.18	.....	
		.....	.....	57.06	.....	
1915	Glickman.....	.....	.....	44.20	.....	
		.....	.....	54.70	.....	
		.....	.....	55.00	.....	
		.....	.....	55.30	.....	
		.....	.....	55.50	.....	
		.....	.....	57.10	.....	
		.....	.....	58.60	.....	
		.....	.....	68.20	.....	
		.....	.....	69.20	.....	

TABLE 92—Yield of oleoresin as obtained in the laboratory.

Date	Observer	Yield of oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Benzin	
		Per ct.	Per ct.	Per ct.	Per cent	
1910	DuMez & Netzel.	78.13	68.42	66.71	14.46	Represents the yield obtained using a Soxhlet's extraction app. except in the case of alcohol.

*Chemistry of the Drug and Oleoresin**Tabulation of Constituents*

The chemistry of lupulin<sup>1</sup> *per se* has received comparatively little attention, although, a very considerable knowledge concerning its constituents has been gained through the work of the brewing chemists and others<sup>2</sup> on hops. The isolation of the

<sup>1</sup> The following have reported more or less complete analyses of lupulin: Ives, Silliman's Am. Journ. of Science (1820), 2, p. 303; Payen, Pelletan and Chevallier, Journ. de Pharm. et de Chim. (1822), 8, p. 209; Personne, *Ibid.* (1854), 59, p. 329; Chapman, The Hop and its Constituents. The Brewing Review, London, (1905).

<sup>2</sup> Power, Tutin and Rogerson, who have completed one of the most recent as well as extensive pieces of work on the constituents of the hop, have isolated the following substances:

## I Volatile oil

## II Alcoholic Extract soluble in water:

1. Choline ( $C_5H_{15}O_2N$ )
2. l-Asparagine ( $C_4H_8O_5N_2$ )
3. Potassium nitrate
4. Tannin
5. Sugar forming a d-phenylhydrazone, m. p. 208.
6. Amorphous bitter material.
7. Volatile base having a coniline-like odor.

## III Alcoholic extract insoluble in water:

1. Hentriacontane ( $C_{31}H_{64}$ )
2. Ceryl alcohol ( $C_{27}H_{56}O$ )
3. Phytosterol ( $C_{27}H_{48}O$ )
4. A phytosterolin, phytosterol glucoside ( $C_{31}H_{56}O_2$ )
5. Volatile fatty acids: formic, acetic, butyric, valeric,  $\beta$ -isopropylacrylic ( $C_5H_8O_2$ ), and nonolic.
6. Saturated and unsaturated non-volatile acids: palmitic, stearic, cerotic, an isomeride of arachidic ( $C_{26}H_{48}O_2$ ), cluytinic and linolic.
7. A new bitter crystalline phenolic substance, humulol ( $C_{17}H_{16}O_2$ )
8. A new tasteless crystalline phenolic substance, xanthohumol ( $C_{13}H_{14}O_2$ )

Journ. Chem. Soc. (1913), 103, p. 1267.

following constituents of pharmaceutical interests has been reported: Volatile oil, resin, wax, alkaloids and inorganic substances. Chapman<sup>3</sup> gives the composition of the ethereal extract as follows:

$\alpha$ -resin .....	18.06 per cent.
$\beta$ -resin .....	67.74 " "
Wax .....	0.28 " "
Other constituents (fat, oil, $\gamma$ -resin, etc.) .....	13.64 " "
Ash .....	0.27 " "

### *Occurrence and Description of Individual Constituents.*

**Volatile Oil.**<sup>4</sup> The volatile oil obtained by distillation with steam is a pale yellow, or colorless, mobile liquid possessing a fragrant and characteristic odor, and a slightly burning taste. It is almost insoluble in water, to which, however, it imparts its odor, and only slightly soluble in dilute alcohol. It is soluble in ether, petroleum ether, chloroform and the other volatile oil solvents. The specific gravity at 20°C is 0.8357 to 0.8776, and the specific rotatory power,  $[\alpha]_D^{20}$ , is 0.20 to 0.58.<sup>5</sup>

According to Chapman,<sup>6</sup> the oil is composed of the terpene, myrcene, ( $C_{10}H_{16}$ ), 40 to 50 per cent; inactive linalool, a fraction of 1 per cent; linalyl isononoate, a fraction of 1 per cent; the sesquiterpene, humulene<sup>7</sup> ( $C_{15}H_{24}$ ), about 40 per cent; and probably some ether of geraniol with a small amount of a diterpene. Rabak,<sup>8</sup> who has more recently completed an investigation of the constituents of the oil, states that, in addition to myrcene and humulene, the oil contains the heptoic, octoic and nonoic acid esters of myrcenol with traces of free fatty acids and probably some free alcohols.

As much as 2 per cent of volatile oil has been obtained from lupulin by steam distillation.<sup>9</sup>

**Resin.** The chemical constitution of the so-called "hop resins" is still an unsolved problem, the literature being replete

<sup>3</sup> *Ibid.*, p. 81. The hop and its constituents. The Brewing Review, London (1905).

<sup>4</sup> The following references are to the earlier literature on the volatile oil: Payen, Pelletan and Chevallier and Personne, l. c.; Wagner, *Journ. f. prakt. Chem.* (1853), 58, p. 351; Ossipon, *Ibid.* (1886), 142, p. 238.

<sup>5</sup> Chapman, l. c.

<sup>6</sup> *Ibid.*

<sup>7</sup> E. Deussen, who has determined the constitution of humulene, finds it to be 1-caryophyllene. *Journ. f. prakt. Chem.* (1911), 83, p. 483.

<sup>8</sup> *Journ. Agric. Research* (1914), 2, p. 115.

<sup>9</sup> Payen, Pelletan and Chevallier, l. c. See also Semmler, l. c.

with vague and contradictory statements.<sup>10</sup> For practical purposes, the classification of Hayduck<sup>11</sup> appears to be the most useful. This investigator distinguishes three resins, which he designates  $\alpha$ ,  $\beta$  and  $\gamma$ , according to their solubility in petroleum ether and their behavior toward a solution of lead acetate. The  $\alpha$ - and  $\beta$ -resins are soluble in petroleum ether, and are further known as the "soft resins," being of a soft consistence at the ordinary temperature. The  $\gamma$ -resin is insoluble in petroleum ether, but soluble in ether or alcohol. It is also known as the "hard resin."

The soft resins are supposed to contain the valuable bitter substances present in hops. From these resins, Lintner and Schnell<sup>12</sup> isolated two crystalline bitter substances of an acid nature. One of these,  $C_{15}H_{24}O_4$ , they proposed naming "humulon;"<sup>13</sup> the other, they have designated "lupulic acid."<sup>14</sup>

According to Chapman, the total resins constitute more than 55 per cent. of the lupulin.<sup>15</sup>

*Wax.* According to Lerner<sup>16</sup> the wax is insoluble in 90 per cent alcohol and can be obtained by treating the ethereal extract with this solvent. He identified it as myricyl palmitate. As Power, Tutin and Rogerson<sup>17</sup> report the presence of ceryl alcohol and cerotic acid in hops, it is quite probable that ceryl cerotate is also a constituent of the wax.

*Alkaloids.* Choline<sup>18</sup> ( $C_5H_{15}O_2N$ ) is the only base occurring in lupulin, the identity of which has been established. There is, however, considerable evidence of the presence of a volatile

<sup>10</sup> The theory advanced by Seyffert (Zeitschr. ges. Brauw. (1896), 19, p. 1 namely, that the hop resins are mixtures of substances in a progressive state of change is probably correct. Confirmation of this theory is to be found in the work of Russell who states that a portion of the "soft resin" is converted into the "hard resin" upon keeping the hops in storage. U. S. Dept. Agric., Bull. No. 282 (1915), p. 9.

<sup>11</sup> Wochenschr. f. Brau. (1887), 4, p. 397; *Ibid.* (1888), 5, p. 937.

<sup>12</sup> Zeitschr. ges. Brauw. (1904), 27, p. 666.

<sup>13</sup> "Humulon" is very likely identical with the "hop-bitter acid" of H. Bungeger, (Bull. Soc. Chim. (1886), 45, p. 487), and the " $\alpha$ -lupulic acid" of Barth. Zeitschr. ges. Brauw. (1900), 23, pp. 509, 537, 554, 572 and 594.

<sup>14</sup> "Lupulic acid" corresponds to the " $\beta$ -lupulic acid" of Barth, *l. c.*

<sup>15</sup> *l. c.*

<sup>16</sup> Dingler's Polytech. Journ. (1863), 169, p. 54.

<sup>17</sup> *l. c.*

<sup>18</sup> Griess and Harrow have shown that hops contain not over 0.02 per cent. of choline. Ber. der deutsch. chem. Ges. (1885), 18, p. 717.

alkaloid possessing a coniine-like odor. Griessmayer,<sup>19</sup> who first noted its presence, gave it the name "lupuline."

In 1885, Williamson<sup>20</sup> reported the isolation of a crystalline alkaloid from wild American hops. He gave it the name "hopeine," and assigned to it the formula,  $C_{18}H_{20}NO_4 \cdot H_2O$ . Ladenburg,<sup>21</sup> who examined a sample of the material thought it to be a mixture of morphine and a more soluble base.<sup>22</sup> As further work<sup>23</sup> along this line has failed to confirm the findings of Williamson, the presence of a crystalline alkaloid must be considered doubtful.

*Ash.* Analyses of the ash of lupulin have apparently not been reported to date. However, Wehmer<sup>1</sup> states that Ca, Cl and  $SiO_2$  are present in the ash from all parts of the hop plant, and, as Na, Mg, Fe, Al, and  $H_3PO_4$  were identified in the ash of the oleoresins examined in the laboratory, it is quite probable that the constituents of lupulin ash are identical with those present in the ash of hops.<sup>2</sup>

There is a great variation in the quantity of ash obtained from commercial samples of lupulin owing to contamination with sand and other earthy matter. Barth<sup>3</sup> gives the yield of ash as 9.5 to 24.4 per cent, while Flueckiger<sup>4</sup> states that a good sample of lupulin should give about 7.0 per cent. According to Keller,<sup>5</sup> lupulin, washed free from all earthy matter, yielded only 2.37 per cent. of ash.

### *Constituents of Therapeutic Importance.*

There appears to be considerable doubt at the present time as to the value of the oleoresin of lupulin as a therapeutic agent. The presence of the soluble bitter principles is said to

<sup>19</sup> Dingler's Polytech. Journ. (1874), 212, p. 67. See also Power, Tutin and Rogerson, l. c.

<sup>20</sup> Pharm. Ztg. (1885), 30 p. 620.

<sup>21</sup> Ber. der deutsch. Chem. Ges. (1886), 19, p. 783.

<sup>22</sup> Williamson, in a second publication, agrees with the findings of Ladenburg and assigns the name hopeine to the more soluble base. Chem. Zeit. (1886), 10, p. 491.

<sup>23</sup> Greshoff could not obtain a crystalline alkaloid from lupulin. Dingler's Polytech. Journ. (1887), 266, p. 316.

<sup>1</sup> Wehmer, *Die Pflanzenstoffe*. Jena. (1911), p. 160.

<sup>3</sup> Richardson, in an examination of hop ash, identified the elements, Na, K, Ca, Mg, Al and Fe, and the acids,  $H_3PO_4$ ,  $H_2CO_3$ , and  $H_2SiO_3$ . Wochenschr. Brau. (1898), 15, p. 160.

<sup>4</sup> Zeitschr. ges. Brauw. (1900), 23, p. 509.

<sup>4</sup> Flueckiger, *Pharmakognosie des Pflanzenreiches*. Berlin (1891), p. 257.

<sup>5</sup> Pharm. Ztg. (1889), 34, p. 533.

impart to it the properties of a simple bitter.<sup>1</sup> The somewhat general belief that the oleoresin is a mild sedative does not appear to be well founded and is probably based on the doubtful report that hops contain an alkaloid (hopeine) resembling morphine in physiological action.<sup>2</sup>

### *Physical Properties*

**Color:** When spread out in a thin layer on a white porcelain surface, the color of the oleoresin was observed to be a dark brown resembling very much that of the oleoresin of ginger.

**Odor:** The preparation when made with acetone or ether has the peculiar odor of lupulin. The odor of the commercial product, however, is often quite different. In some cases it is disagreeable and resembles valeric acid,<sup>3</sup> while in other cases it is pleasant and suggests the presence of the ethyl esters of the lower fatty acids.<sup>4</sup>

**Taste:** The taste is bitter and somewhat aromatic resembling that of lupulin.

**Consistence:** The oleoresin, when prepared according to the directions of the *United States Pharmacopœia* of 1900 is of the consistence of a very soft extract. On standing in partially filled containers, it becomes firmer as a result of the conversion of a part of the soft resin into hard resin.

**Solubility:** The official preparation is freely soluble in alcohol (95 per cent.), acetone, ether, chloroform and glacial acetic acid. It is partially soluble in petroleum ether, the extent of its solubility depending on the age of the oleoresin (if stored in partially filled containers) or on the age of the drug from which the latter is prepared.<sup>5</sup> It is also slightly soluble in hot water to which it imparts a bitter taste.

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<sup>1</sup> Potter, *Mat. Med., Pharm. & Therap.* (1903), p. 339.

<sup>2</sup> *Pharm. Ztg.* (1885), 30, p. 620.

<sup>3</sup> This is due to the use of old deteriorated drug in the preparation of the oleoresin or to the storing of the latter under improper conditions. See under "Drug used, its collection, preparation, etc."

<sup>4</sup> The agreeable fruity odor sometimes noticed is thought to be due to the presence of ethyl esters of the lower fatty acids formed as a result of the extraction of old deteriorated drug with alcohol.

<sup>5</sup> On aging under ordinary conditions, the soft resin present in the drug or oleoresin is converted, in part, into hard resin. As only the former is soluble in petroleum ether, old oleoresins, or those prepared from old drug, are usually less soluble in this solvent than the preparations freshly made from unaltered drug. See under "Drug used, its collection, preservation, etc."



*Specific gravity:* The oleoresin has the highest specific gravity of any of the preparations of this class, specific gravities of 1.065 and 1.067 having been observed for the same when made with ether and acetone, respectively. Alcohol yields a product of somewhat greater density, whereas the use of petroleum ether gives an oleoresin of low specific gravity. The important factors influencing the specific gravity of this oleoresin, aside from the effect produced by the use of different solvents in its preparation, are thought to be the condition of the drug<sup>1</sup> when extracted and the presence of unevaporated solvent in the finished product. The results obtained in the examination of laboratory and commercial samples are given in the following tables.

TABLE 93—*Specific gravities of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Specific gravity
				At 25° C
1	1910	DuMez & Netzel.....	Alcohol.....	1.089
2	"	" "	Acetone.....	1.067
3	"	" "	Ether.....	1.065
4	"	" "	Benzin.....	1.037

TABLE 94—*Specific gravities of commercial oleoresins.*

Sample No.	Date	Observer	Source	Specific gravity
				At 25° C
1	1916	DuMez.....	Sharp & Dohme.....	1.065
2	"	".....	Squibb & Sons.....	1.083 <sup>1</sup>
3	"	".....	Lilly & Co.....	1.066

<sup>1</sup> The preparation had a slight odor of ether.

*Refractive index:* The refractive index of the oleoresin, when prepared with acetone, was found to be 1.516 at 25°C, which agrees fairly well with that obtained for the sample from Sharp and Dohme. The low refractive index observed for the sample from Lilly and Co. is thought to be due to the presence of un-

<sup>1</sup> See under the caption "Chemistry of the drug and oleoresin".

evaporated solvent (probably alcohol). The results obtained in the determinations made in the laboratory are given in the tables which follow:

TABLE 95—*Refractive index of the oleoresin prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Refractive index
				At 25° C
1	1916	DuMez.....	Acetone .....	1.5163

TABLE 96—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
				At 25° C
1	1916	DuMez.....	Lilly & Co.....	1.496
2	"	" .....	Sharp & Dohme.....	1.519

### *Chemical Properties.*

*Loss in weight on heating:* A loss in weight of 9.59 to 15.63 per cent. was observed for the laboratory preparations when heated at 110°C. Except in the case of the oleoresin which contained unevaporated solvent (alcohol), the loss did not exceed 10.32 per cent. Results of a similar magnitude were obtained for the commercial samples examined as is shown in the tables which follow.

TABLE 97—*Laboratory preparations—loss in weight on heating.*

Sample No.	Date	Observer	Solvent	Per cent. of loss on heating
				At 110° C
1.....	1916	DuMez.....	Alcohol .....	15.63 <sup>1</sup>
2.....	"	" .....	Acetone .....	9.59
3.....	"	" .....	Ether .....	10.32
4.....	"	" .....	Benzin.....	10.06

<sup>1</sup> Contained unevaporated solvent.

TABLE 98—Commercial oleoresins—loss in weight on heating.

Sample No.	Date	Observer	Source	Per cent. of loss on heating
1.....	1916	DuMez.....	Sharp & Dohme.....	At 110° C 7.22
2.....	"	".....	Squibb & Sons.....	9.46
3.....	"	".....	Lilly & Co.....	20.68

<sup>1</sup> Contained ether.<sup>2</sup> Probably contained unevaporated solvent (alcohol).

**Ash content:** The ash contents, in the case of the oleoresins prepared in the laboratory, were found to be 0.93, 1.46 and 1.82, depending on whether ether, acetone or alcohol was employed in their preparation. A somewhat similar variation in the amount of ash obtained for the commercial samples examined is, therefore, taken to be an indication of the indiscriminate use of the above-mentioned solvents in their manufacture, instead of acetone as was directed to be employed by the 1900 edition of the *United States Pharmacopæia*. The slightly higher values obtained for the commercial samples may have been due to the copper, which was found to be present in considerable amounts. The results obtained in the ash determinations made in the laboratory follow:

TABLE 99—Ash contents of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Per cent. of ash
1.....	1916	DuMez.....	Alcohol.....	1.62
2.....	"	".....	Acetone.....	1.46
3.....	"	".....	Ether.....	0.93
4.....	"	".....	Petrol. ether.....	0.08

TABLE 100—Ash contents of commercial oleoresins.

Sample No.	Date	Observer	Source	Per cent. of ash	Foreign constituents
1.....	1916	DuMez.....	Squibb & Sons.....	0.87 <sup>1</sup>	Copper
2.....	"	".....	Lilly & Co.....	1.53 <sup>2</sup>	"
3.....	"	".....	Sharp & Dohme.....	1.71	"

<sup>1</sup> Contained ether.<sup>2</sup> Probably contained unevaporated solvent (alcohol).

*Acid number:* The acid numbers given in the first of the tables which follow are those obtained for preparations which had stood in the laboratory for six years previous to being examined. As the acidity of the oleoresin very likely increases on ageing, when kept under ordinary conditions, due to the oxidation of some of its constituents, it is thought that a somewhat lower value is to be expected for this constant in the case of the freshly made preparation. The relatively low value found for the oleoresin prepared with alcohol was due to the presence of unevaporated solvent, which not only acts as a diluent, but also combines to some extent with the acids present forming esters, the latter imparting a fruity odor to the preparation. Viewed in the light of the foregoing statements, the acid numbers obtained for the commercial samples indicate that two of them were very probably old preparations and that the third (the sample obtained from Lilly & Co.) contained unevaporated solvent (alcohol). The results obtained in the determination of this constant in the laboratory follow.

TABLE 101—*Acid numbers of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Acid number
1.....	1916	DuMez.....	Alcohol.....	62.9 <sup>1</sup>
2.....	"	" .....	Acetone .....	84.1
3.....	"	" .....	Ether .....	80.1
4.....	"	" .....	Benzin.....	79.7

<sup>1</sup> Contained unevaporated solvent.

TABLE 102—*Acid numbers of commercial oleoresins.*

Sample No.	Date	Observer	Source	Acid number
1.....	1916	DuMez.....	Lilly & Co. ....	61.7
2.....	"	" .....	Sharpe & Dohme.....	85.5
3.....	"	" .....	Squibb & Sons.....	78.4 <sup>1</sup>

<sup>1</sup> Contained ether.

*Saponification value:* Saponification values ranging from 223.4 to 239.6 were obtained for the oleoresins prepared in the laboratory, the variation being due, very likely, to the nature of the solvent employed in extracting the drug. The values found

for the commercial preparations were somewhat lower, due, in two cases, to the presence of unevaporated solvent. In the third instance, the low saponification value obtained was very probably due to a difference in the quality of the lupulin from which the oleoresin was extracted. The results obtained in the examination of laboratory and commercial preparations follow.

TABLE 103—*Saponification values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Saponification value
1	1916	DuMez.....	Alcohol.....	223.4 <sup>1</sup>
2	"	".....	Acetone.....	239.6
3	"	".....	Ether.....	230.8
4	"	".....	Benzin.....	227.4

<sup>1</sup> Contained ether.

TABLE 104—*Saponification values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Saponification value
1	1916	DuMez.....	Lilly & Co.....	158.8 <sup>1</sup>
2	"	".....	Sharp & Dohme.....	220.0
3	"	".....	Squibb & Sons.....	223.3 <sup>2</sup>

<sup>1</sup> Probably contained unevaporated solvent (alcohol).

<sup>2</sup> Contained ether.

*Iodine value:* The oleoresin, when prepared with acetone, ether, or benzin, was found to have an iodine value varying from 94.7 to 96.2. When alcohol was the solvent employed in its preparation, the value obtained was considerably lower, namely, 82.05. A comparison of these values with those found for the commercial samples indicates that alcohol is sometimes used in their preparation. The extremely low value obtained for the oleoresin of Lilly & Co. is to be attributed to the presence of unevaporated solvent (alcohol) as well as to the effect produced by its use as a menstruum. The iodine values obtained for the preparations examined in the laboratory are given in the tables which follow.

TABLE 105—Iodine values of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Iodine value
1.....	1916	DuMez.....	Alcohol.....	82.05 <sup>1</sup>
2.....	"	".....	Acetone.....	96.2
3.....	"	".....	Ether.....	94.7
4.....	"	".....	Benzin.....	95.7

<sup>1</sup> Alcohol was present.

TABLE 106—Iodine values of commercial oleoresins.

Sample No.	Date	Observer	Source	Iodine value
1.....	1916	DuMez.....	Lilly & Co.....	88.7 <sup>1</sup>
2.....	"	".....	Sharp & Dohme.....	92.9
3.....	"	".....	Squibb & Sons.....	91.5 <sup>2</sup>

<sup>1</sup> Alcohol was probably present.<sup>2</sup> The odor of ether was noticeable.

### Adulterations.

Adulteration effected through the use of old deteriorated drug in the manufacture of this preparation has been noted. See under "Drug used, its collection, preservation, etc."

The presence of copper was detected in all of the commercial samples examined. See under "Ash content."

## OLEORESIN OF PARSLEY FRUIT

### Synonyms

*Aetherisches Petersilieextrakt*, Culbreth, Mat. Med. (1917), p. 428.

*Green Apiol*,<sup>1</sup> Brit. Pharm. Cod. 1907.

*Oil of Parsley*, Parrish. Treat. on Phar. (1867), p. 757.

*Oleoresina Petroselinæ*, U. S. P. 1910.

*Oléorésine de Persil*, Culbreth, Mat. Med. (1917), p. 428.

*Liquid Apiol*, Brit. Pharm. Cod. 1907.

<sup>1</sup> "Green apiol" is stated to be an alcoholic extract of the parsley fruit; "yellow apiol," the product obtained on treating this extract with animal charcoal, or upon saponifying the same with lead oxide; and "white apiol" the volatile oil obtained on distilling the extract with steam. Brit. and Col. Drugg. (1910), 58, p. 235.

The compound,  $C_{12}H_{14}O_4$ , spoken of in chemical literature as apiol is known commercially as crystalline apiol. Brit. Pharm. Cod. (1907), p. 112.

### History.

The oleoresin of parsley appears to have come into existence through the attempts which were made to discover a simple method for the preparation of the so-called "apiol" of Homolle and Joret,<sup>1</sup> which was first brought to the attention of the pharmacist in 1855. The first mention of the oleoresin, insofar as could be determined with the information at hand, is to be found in Parrish's Treatise on Pharmacy published in 1867. Since that time, the preparation, or one of a similar nature, has been on the market under the name of "green apiol" or "liquid apiol," but was never given official recognition until the appearance of the present edition of the *United States Pharmacopoeia*.

### Drug Used, Its Collection, Preservation, Etc.

In the present edition of the *United States Pharmacopoeia*, parsley fruit is defined as follows: "The dried ripe fruit of *Petroselinum sativum* Hoffman (Fam. *Umbelliferae*), without the presence or admixture of more than 5 per cent. of foreign seeds or other matter. Preserve Parsley Fruit carefully in tightly-closed containers protected from light." The plant from which the fruit is obtained has also been known under the following botanical synonyms: *Carum Petroselinum* Benth. and Hook., and *Apium Petroselinum* Linné.

Parsley is an annual herb commonly cultivated in the gardens of Europe and America. The fruit ripens in the fall, when it is gathered, dried and preserved for domestic use or shipped to market. The fruit as found in the market shows no marked difference in appearance regardless of its source. However, it is known to differ in its chemical composition. Thus, the fruits grown in Germany contain apiol as the principal constituent of therapeutic importance, whereas, those grown in France contain myristicin.<sup>2</sup> The volatile oil content also appears to vary with the source as Flueckiger<sup>3</sup> states that the

<sup>1</sup> The "apiol" of Homolle and Joret is stated to be the product which remains unsaponified when the ether or chloroform soluble portion of the alcoholic extract of parsley fruit is heated with litharge. Journ. de Pharm. et de Chim. (1855), 28, p. 212.

<sup>2</sup> See under "Chemistry of parsley fruit".

<sup>3</sup> *Pharmakognosie des Pflanzenreichs* (1891), p. 938.

fruits grown in Norway have an exceptionally strong odor. Both of the foregoing variations in the composition of the drug would naturally be imparted in an increased degree to the oleoresins prepared therefrom. As the chemistry of the American fruit does not appear to have been studied, its value in this connection cannot be said to be definitely established. There is good reason, however, to believe that the oleoresins made in this country, in part at least, are prepared from home grown fruits.<sup>1</sup>

The large amount of fixed and volatile oils present in these fruits requires that they be preserved in tightly closed containers protected from the light.

### *U. S. P. Text and Comments Thereon.*

The oleoresin was given official recognition for the first time by being admitted to the late edition of the *United States Pharmacopœia* (edition of 1910).

1910

#### Oleoresina Petroselini

#### Oleoresin of Parsley Fruit

#### Oleores. Petrosel.—Liquid Apiol

Parsley Fruit,<sup>1</sup> in No. 60 powder,<sup>2</sup> tillation on a water-bath,<sup>3</sup> and, having five hundred grammes . . . 500 Gm. ing transferred the residue to a dish, Ether,<sup>4</sup> a sufficient quantity. remove the remaining ether by spontaneous evaporation in a warm place,

Place the parsley fruit in a cylindrical glass percolator provided with a stop-cock and arranged with a receptacle suitable for volatile liquids.<sup>4</sup> Pack the powder firmly, and percolate slowly with ether, and preserve it in well-stoppered bottles.<sup>5</sup> Allow the oleo-resin to stand without agitation for four or five days, decant the clear liquid portion from any solid residue,<sup>6</sup> and recover the drug is exhausted.<sup>5</sup> Recover the

greater portion of the ether by distillation. Average Dose.—Metric, 0.5 mil—Apothecaries, 8 minims.

1) For a description of the drug, see page 1104 under "Drug used, its collection, preservation, etc."

2) The Pharmacopœia directs that the fruit be reduced to a

<sup>1</sup> Joseph K. Janks in his book on spices states that parsley is being grown in this country. Jos. K. Janks, *Spices*, New York (1915), p. 69.

<sup>2</sup> Oulbreth on page 428 of the 1917 edition of his work on *Materia Medica* also refers to the cultivation of parsley in the United States.



No. 60 power for percolation. Owing to the large fatty oil content, this degree of fineness is difficult to attain, and, as experiments conducted in the laboratory indicate that a No. 40 powder is equally satisfactory for this purpose, it appears that a change to this effect in the pharmacopœial directions is desirable.

3) Ether is the solvent directed by the Pharmacopœia to be used for the extraction of the substances constituting the oleoresin. Observations made in the laboratory indicate that other solvents may also be employed for this purpose without in any way detracting from the value of the finished product. Thus, acetone and petroleum ether were found to yield products almost identical with that obtained by the use of ether. The latter is to be preferred to benzin as suggested by Beringer (1892) since its composition is more constant. Alcohol which is used commercially in the preparation of some of the so-called liquid apiols dissolves a considerable amount of coloring matter and other inert substances and, therefore, yields a product of inferior quality.

4) For a description of the various forms of percolators which have been designed to meet the specifications of the Pharmacopœia, see Part I under "Apparatus used".

5) The pharmacopœial directions governing the extraction of the oleoresinous material are to slowly percolate the drug with ether, added in successive portions, until complete exhaustion has been effected. Here again, the use of some form of continuous extraction apparatus would appear to be an improvement over the present method.

6-7) For comments on this step in the pharmacopœial method of preparation, see under comments on the oleoresin of cubeb.

8) Upon the complete removal of the solvent from the percolate, the residual oily liquid deposits a small amount of waxy matter which the Pharmacopœia directs shall be removed by decantation. When either is the solvent used in extracting the drug, this deposit amounts to less than 1 per cent of the oleoresin, while the percentage is somewhat greater, about 1.5 per cent when acetone is used. The deposit resulting when benzin was the solvent employed was found by Beringer to be equal to about 3 per cent.

9) The oleoresin should be kept in well-stoppered bottles as

it loses volatile oil upon exposure to the air, and as the glycerides are prone to undergo partial decomposition due to the action of the moisture and oxygen.

### *Yield.*

The information at hand is not sufficient to permit of a statement being made as to what the average yield of oleoresin should be in this case. The results obtained in the laboratory and those reported by Beringer show that it is at least 24 per cent., when ether or acetone are the solvents employed in extracting the drug, whereas those reported by Vanderkleed would appear to indicate that the yield is much lower. The available information of this nature is given in the following tables:

TABLE 107—*Yield of oleoresin as reported in the literature.*

Date	Observer	Yield of Oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Other Solvents	
		Per cent.	Per cent.	Per cent.	Per cent.	
1892..	Beringer.....	.....	24.0	.....	Benzin 19.3	The total yield of extractive matter to benzin is given as 22.3 per cent. which includes 3 percent. of deposited wax.
1913..	Vanderkleed ...	.....	.....	.....	Solvent (?) 11.40	
	" .....	.....	.....	.....	13.04	Reported as yield of oleoresin.
	" .....	.....	.....	.....	14.70	

TABLE 108—*Yield of oleoresin as obtained in the laboratory.*

Date	Observer	Yield of oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per ct.	
1916	DuMez.....	.....	28.89	29.17	.....	Represents the yield using a Soxhlet's Extraction App.

*Chemistry of the Drug and Oleoresin.**Enumeration of Constituents.*

The following are the known constituents of parsley fruit which may be considered of pharmaceutical interest; volatile oil, fatty oil, apiin, and inorganic substances. While analyses of the oleoresin have not been reported, the first two named constituents of the fruit, together with a small amount of inorganic matter, very likely represent this preparation when made by extracting the drug with ether, as apiin is stated to be insoluble in this solvent.

*Occurrence and Description of Individual Constituents.*

**Volatile Oil.**<sup>1</sup> The volatile oil of parsley fruit is described as a colorless or yellowish, thick liquid having a specific gravity of 1.03 to 1.10 at 15°C. The angle of rotation in a 100 millimeter tube is given as -5° to -10°. It is soluble in alcohol, ether, chloroform and petroleum ether. On cooling or shaking with water, it precipitates apiol.<sup>2</sup>

The composition of the oil varies with the locality in which the fruit is grown. The principal constituent of the oil distilled from the fruit grown in Germany is apiol. Myristicin is present only in very small quantities.<sup>3</sup> It is stated that the apiol content is often so great that the oil is a semi-solid at ordinary temperatures. In the French oil, myristicin predominates, while apiol, together with allyltetramethoxybenzene, is present in small amount.<sup>4</sup> The constitution of these compounds is represented by the following formulas:

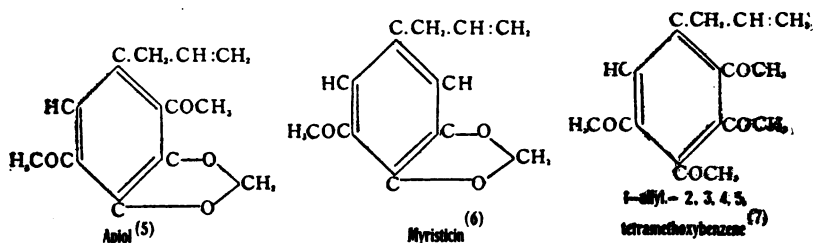
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<sup>1</sup> The following list comprises the more important references to the earlier literature on the volatile oil: Bley, Trommsdorff's neues Journ. (1827), 14, p. 134; Bolle, Arch. der Pharm. (1829), 29, p. 168; Blanchet and Sell, Ann. der Chem. (1833), 6, p. 301; Loewig and Weidmann, *Ibid.* (1839), 32, p. 283; von Gerichten, Ber. der. deutsch. chem. Ges. (1876), 9, pp. 258 and 1477.

<sup>2</sup> Schimmel & Co., Ber. (1906), p. 95.

<sup>3</sup> Thoms, Ber. der deutsch. chem. Ges. (1903), 36, p. 3451; *Ibid.* (1908), 41, p. 2753; Chevalier, Bull. sci. pharmacologique (1910), 17, p. 128; Chem. Abs. (1911), 5, p. 1490.

<sup>4</sup> *Ibid.* Also, Bignami and Testoni, Gaz. Chim. ital. (1900), 30, p. 240.



Apiol is a crystalline solid possessing in a strong degree the odor of parsley. Its melting point is 30°C and the boiling point 294°C.<sup>8</sup> Eykman<sup>9</sup> gives the specific gravity at 14°C as 1.176, and the refractive index  $[n]_D$  as 1.538. It is soluble in alcohol, ether, chloroform and oils. It also dissolves in concentrated sulphuric acid, the solution formed being blood-red in color.

Myristicin is a liquid possessing but little odor. It does not solidify even when cooled to a comparatively low temperature. Semmler<sup>10</sup> gives the specific gravity as 1.141 at 25°C. Its solubility is similar to that of apiol.

In addition to the foregoing, Thoms<sup>11</sup> reports the presence of the following in both, the German and French oils: l-pinene, phenols and palmitic acid.

Semmler<sup>12</sup> reports the volatile oil content of parsley fruit to be 2 to 6 per cent.

**Fatty Oil.**<sup>13</sup> The fatty oil of parsley fruit is a greenish yellow mobile liquid. It is soluble in a mixture of alcohol and ether, in ether, chloroform and carbon disulphide. A sample from Schimmel & Co., examined by von Gerichten and Koehler,<sup>14</sup>

<sup>8</sup> Eykman, Ber. der. deutsch. chem. Ges. (1890), 23, p. 862; Thoms, *Ibid.* 1903, 36, p. 174.

<sup>9</sup> Thoms. Chem. Ztg. (1903), 27, p. 938.

<sup>11</sup> Thoms. Ber. der. deutsch. chem. Ges. (1908), 41, p. 2761.

<sup>10</sup> Ciamician and Silber, *Ibid.* (1888), 21, p. 1632.

<sup>12</sup> l. c.

<sup>13</sup> Semmler, *Die aetherische Oele* (1907), 4, p. 168.

<sup>14</sup> *Arbeiten aus d. Pharm. Inst., Univ. Berlin* (1909), 6, p. 190.

<sup>15</sup> Semmler, *Die aetherische Oele* (1907), 4, p. 173.

<sup>16</sup> Grimme obtained 16.7 per cent. of a red-brown oil having the following properties: specific gravity at 15°C, 0.9243; refractive index at 35°C, 1.4778; saponification value, 176.5; iodine value, 109.6; acid value, 3.4; unsaponifiable matter, 2.18 per cent. He was unable to obtain a test for the presence of phytosterin in the unsaponifiable residue. Pharm. Centralh. (1911), 52, p. 663.

<sup>17</sup> Ber. der. deutsch. chem. Ges. (1909), 42, p. 1638.

showed the following properties: specific gravity at 15°C, 0.972; refractive index at 40°C, 1.4624; saponification value, 190.9; iodine value, 80.07.

The saponifiable portion of the oil was found to be composed of the glyceryl esters of oleic, palmitic, stearic and petroselinic acids. The latter is stated to be isomeric with oleic acid. From the unsaponifiable residue, Matthes and Heintz<sup>15</sup> isolated a hydrocarbon,  $C_{26}H_{42}$ , to which they gave the name petrosilan; also, myricyl alcohol and a mixture giving a test for phytosterin.

The average fatty oil content of the fruit is probably about 20 per cent.<sup>16</sup>

*Apiin.*<sup>17</sup> Apiin ( $C_{27}H_{32}O_{16}$ ) is a glucoside. Its melting point is stated to be 228°C. On hydrolysis, it yields a sugar and apigenin (trioxyflavon)  $C_{15}H_{10}O_5$ . It is soluble in hot alcohol or water, insoluble in ether, and therefore, it is not likely to be present in the oleoresin.

*Ash.* Available information concerning the constituents of the ash of parsley fruit is limited to the analysis of Rump,<sup>18</sup> who reports the presence of the basic elements, K, Ca, Mg and Fe in combination with the acids, HCl,  $H_2SO_4$ ,  $H_3PO_4$ ,  $H_2CO_3$  and  $H_2SiO_3$ , also, some free  $SiO_2$ .

The ash content<sup>19</sup> of parsley fruit is about 6.50 to 7.00 per cent. Commercial samples sometimes show a higher percentage of ash due to contamination with foreign matter.<sup>20</sup>

### *Constituents of Therapeutic Importance.*

The oleoresin of parsley fruit is said to be used chiefly as an emmenagogue. Such being the case, its therapeutical value is undoubtedly due to the volatile oil which it contains as both apiol<sup>1</sup> and myristicin,<sup>2</sup> constituents of the essential oil, have

<sup>15</sup> Ber. der. pharm. Ges. (1909), 19, p. 325.

<sup>16</sup> Rump, obtained 22 per cent. of fatty oil. Buchner's Repert. f. d. Pharm. (1836), 6, p. 6. Grimme gives the yield as 16.7 per cent. l. c.

<sup>17</sup> von Gerichten, Ber. der deutsch. chem. Ges. (1876), 9, p. 1121.

<sup>18</sup> Buchner's Repert. f. d. Pharm. (1836), 56, p. 26.

<sup>19</sup> Rump gives the ash content as 6.5 per cent. *Ibid.* Warnecke reports the percentage of ash as 7.04. Pharm. Ztg. (1886), 31, p. 536.

<sup>20</sup> La Wall and Bradshaw report two commercial samples of parsley fruit yielding 6.61 and 9.10 per cent. of ash, respectively. Proc. A. Ph. A. (1910), 58, p. 752.

<sup>1</sup> Heffter, Arch. f. exp. Path. u. Pharmak. (1895), 35, p. 365. Chevalier Bull. Sci. pharmacologique, 17, pp. 128-131.

<sup>2</sup> Juerss, Schimmel & Co., Ber. (1904), p. 159.

been shown to be severe intestinal irritants. The activity of the volatile oil may be further accounted for by the presence of terpenes as these compounds are also known to be irritants.<sup>3</sup>

### *Physical Properties*

**Color:** When spread out in a thin layer on a white porcelain surface, the oleoresin was observed to be greenish-yellow in color. The so-called fluid apiols of commerce, preparations made with alcohol, are of a comparatively deep green color.

**Odor:** The oleoresin has the agreeable aromatic odor of parsley.

**Taste:** The taste is spicy like that of the drug from which it is prepared.

**Consistence:** The oleoresin is a rather thin liquid, being of about the consistence of olive oil.

**Solubility:** The official preparation is soluble in acetone, ether, chloroform, carbon disulphide and petroleum ether. It is almost insoluble in alcohol or water.

**Specific gravity:** The specific gravities of the oleoresins prepared in the laboratory were found to be 0.937 and 0.940 at 25°C. In the making of these preparations ether and acetone, respectively, were employed as menstrua for extracting the drug. The specific gravity of the only commercial sample, conforming in its general properties to the official product, was observed to be about the same, i. e. 0.943. In the case of the other commercial products, the greater density is thought to be due to the use of alcohol in their preparation.<sup>1</sup> The results for the determinations made in the laboratory follow.

TABLE 109—*Specific gravities of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Specific gravity
1.....	1916	Du Mez .....	Acetone.....	At 25° C 0.940
2.....		.....	Ether .....	0.937

<sup>3</sup> Kehler, Arch. f. Gyn. (1910), 90, p. 169.

<sup>1</sup> This statement is also based on the dark green color of the preparations and the fact that alcohol is the solvent mentioned in the literature in connection with the preparation of the so-called fluid apiols. See under "History" of the oleoresin.

TABLE 110—*Specific gravities of commercial oleoresins.*

Sample No.	Date	Observer	Source	Specific gravity
1.....	1916	DuMez.....	Sharp & Dohme.....	At 25° C 0.943
2.....	"	".....	Squibb & Sons.....	0.984 <sup>1</sup>
3.....	"	".....	Merck & Co.....	1.008 <sup>2</sup>

<sup>1</sup> Apiol, fluid,—Squibb.<sup>2</sup> Apiol, fluid, green,—Merck.

*Refractive index:* Observations made in the laboratory indicate that the oleoresin should have a refractive index of about 1.477 at 25°C, when ether or acetone are employed in the extraction of the drug. A result almost identical with the preceding was obtained for the only commercial sample examined. The refractive indices observed in the case of the so-called liquid apiols were somewhat higher, due very likely to the use of alcohol in their preparation. The data given in the following tables illustrate these points.

TABLE 111—*Refractive indices of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Refractive index
1	1916	DuMez.....	Acetone.....	At 25° C 1.477
2	"	".....	Ether.....	1.477

TABLE 112—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
1	1916	DuMez.....	Sharp & Dohme.....	At 25° C 1.475
2	"	".....	Squibb & Sons.....	1.486 <sup>1</sup>
3	"	".....	Merck & Co.....	1.1488 <sup>2</sup>

<sup>1</sup> Apiol, Fluid—Squibb.<sup>2</sup> Apiol, Fluid, Green,—Merck.

*Chemical Properties.*

*Loss in weight on heating:* The oleoresins prepared in the laboratory, using ether and acetone as menstrua for exhausting the drug, lost 7.87 and 7.92 per cent. of their weight, respectively, on heating at 110°C. In the case of the only commercial sample examined, the loss was about one-half as great due very likely to a smaller amount of volatile matter (essential oil) being contained in the drug from which the latter was prepared. The results obtained are given in the tables which follow.

TABLE 113—*Laboratory preparations—loss in weight on heating.*

Sample No.	Date	Observer	Solvent	Per cent. of loss on heating
1.....	1916	DuMez.....	Acetone.....	At 100° C 7.92
2.....	"	".....	Ether.....	7.87

TABLE 114—*Commercial oleoresins—loss in weight on heating.*

Sample No.	Date	Observer	Source	Per cent. of loss on heating
1.....	1916	DuMez.....	Sharp & Dohme.....	At 110° C 8.85

*Ash content:* The results obtained in the determination of the ash content of the oleoresins examined in the laboratory are given in the tables which follow. Aside from the fact that the amount of ash obtained varied with the solvent used in the making of the preparations, the only items of importance brought out by these results are that ether was evidently employed in the manufacture of the commercial product and that the latter contained copper.

TABLE 115—*Ash contents of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Per cent. of ash
1.....	1916	DuMez.....	Acetone.....	0.18
2.....	"	".....	Ether.....	0.09



TABLE 116—*Ash contents of commercial oleoresins.*

Sample No.	Date	Observer	Source	Per cent. of ash	Foreign constituents
1.....	1916	DuMez... ..	Sharp & Dohme.....	0.00	Copper

*Acid number:* The acid numbers obtained for the oleoresins prepared with acetone and ether were found to be 9.3 and 9.2, respectively, indicating that the difference in the nature of the two solvents has but little influence on the value of this constant. The high value found for the sample obtained from Sharp & Dohme is thought to be due to the hydrolysis of some of the glycerides, and, therefore, to indicate an old preparation, or one that has been prepared from old deteriorated drug. The acid numbers obtained for the oleoresins examined, also those found for the so-called liquid apiols, are given in the tables which follow.

TABLE 117—*Acid numbers of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Acid number
1	1916	DuMez.....	Acetone.....	9.3
2	"	".....	Ether.....	9.2

TABLE 118—*Acid numbers of commercial preparations.*

Sample No.	Date	Observer	Source	Acid number
1	1916	DuMez.....	Merck & Co.....	12.1 <sup>1</sup>
2	"	".....	Sharp & Dohme.....	50.5
3	"	".....	Squibb & Sons.....	58.5 <sup>1</sup>

<sup>1</sup> Apiol, Fluid, Green.

*Saponification value:* The saponification values of the oleoresins prepared in the laboratory, using ether and acetone as menstrua for extracting the drug, were found to be 158.5 and 165.6, respectively. The high value (181.6) obtained for Sharp

& Dohme's preparation is thought to be due to the presence of a relatively large amount of the glyceride of petroselinic acid, which is stated by von Gerichten to have a saponification value of 191.2. See under "Chemistry of the drug and oleoresin." Tables showing the saponification values of the preparations examined in the laboratory follow. For comparison with the foregoing data, the values obtained for the so-called liquid apiols have also been included in these tables.

TABLE 119—*Saponification values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Saponification value
1.....	1916	DuMez.....	Acetone.....	165.6
2.....	"	".....	Ether.....	158.5

TABLE 120—*Saponification values of commercial preparations.*

Sample No.	Date	Observer	Source	Saponification value
1.....	1916	DuMez.....	Merck & Co.....	108.5 <sup>1</sup>
2.....	"	".....	Squibb & Sons.....	126.7 <sup>2</sup>
3.....	"	".....	Sharp & Dohme.....	181.6

<sup>1</sup> Apiol, Fluid, Green,—Merck.

<sup>2</sup> Apiol, Fluid,—Squibb.

*Iodine value:* The iodine values as found for the oleoresins prepared in the laboratory are given in the first of the tables which follow. It will be observed that there is a considerable difference in these values due to the nature of the solvent employed in extracting the drug. The low iodine value observed for the preparation made by Sharp & Dohme is to be attributed to the partial oxidation of the unsaturated glycerides. For comparison, the iodine values of two samples of so-called "liquid apiols" (preparations made with alcohol) have been included in the tables which follow.

TABLE 121—Iodine values of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Iodine value
1.....	1916	DuMez.....	Acetone .....	132.5
2.....			Ether .....	122.9

TABLE 122—Iodine values of commercial preparations.

Sample No.	Date	Observer	Source	Iodine value
1.....	1916	DuMez.....	Sharp & Dohme.....	110.6
2.....	"	" .....	Squibb & Sons.....	123.3 <sup>1</sup>
3.....	"	" .....	Merck & Co.....	180.2 <sup>2</sup>

<sup>1</sup> Labeled "Apiol-Fluid."<sup>2</sup> Labeled Apiol, Fluid, Green.

### Adulterations.

A trace of copper was found to be present in the commercial samples examined. See under "Ash content."

### OLEORESIN OF PEPPER

#### Synonyms

*Aetherisches Pfeffereextrakt*, Nat. Disp. 1884.

*Ethereal Extract of Black Pepper*, King's Am. Disp. 1900.

*Extractum Piperis*, Hirsh, Univ. P. 1902, No. 1244.

*Extractum Piperis Fluidum*, U. S. P. 1850.

*Fluid Extract of Black Pepper*, U. S. P. 1850.

*Oil of Black Pepper*, King's Am. Disp. 1900.

*Oleoresina Piperis*, U. S. P. 1900.

*Oléorésine de Poivre noir*, U. S. Disp. 1907.

#### History.

The oleoresin of pepper appears to have been first obtained as a by-product<sup>1</sup> in the preparation of piperine. Thus, Dr. Meli in France as early as 1825, reported having obtained the so-called "oil of black pepper" as a residue on separating the piperine from the alcoholic extract of the drug. The first notice of its use as a therapeutic agent apparently came from

<sup>1</sup> Jourdan, *Univ. P.* (1832), p. 246.

America as Carpenter, in 1829, in an article on Peruvian bark, refers to its use by Dr. Chapman of Philadelphia in connection with the administration of quinine. The oleoresin prepared with ether became official in the *United States Pharmacopœia* in 1850 under the title *Extractum Piperis Fluidum*. In the 1860 edition, the name was changed to *Oleoresina Piperis*, under which title, it is still official at the present time. Neither this preparation nor one of a similar nature has ever been given official recognition abroad.

*Drug Used, Its Collection, Preservation, Etc.*

According to the present edition of the *United States Pharmacopœia*, the drug recognized is "the dried, unripe fruit of *Piper nigrum* Linné (Fam. *Piperaceae*), without the presence or admixture of more than two per cent of stems or other foreign matter." It has also occasionally been referred to under the botanical synonyms, *Piper trioicum* Roxb.

As becomes apparent from the foregoing, only the unripe fruits should be used. As the fruit reaches maturity, the chlorophyll content diminishes and it becomes less pungent.<sup>1</sup> A variation in the chlorophyll would naturally effect the properties of the oleoresin prepared therefrom, while a difference in piperine content would have no significance in this connection as only a small portion of the total piperine (to which pepper owes its pungency)<sup>2</sup> remains in solution in the oleoresin, the greater part being precipitated upon the removal of the solvent.

Pepper, as it occurs on the market, consists of a number of commercial varieties, viz: Malabar, Cochin, Penang, Singapore, Siam and others.<sup>3</sup> The quality of these varieties is ordinarily governed by weight, the Malabar being the heaviest. The Penang, however, is stated to be the most pungent. The manner in which either of these qualities effect the oleoresin does not appear to have been determined. While the *Pharmacopœia* makes no provisions for the preservation of this drug, its volatile oil content necessitates the use of closed containers.

<sup>1</sup> Flueckiger, *Pharmakognosie des Pflanzenreiches* (1891), p. 913.

<sup>2</sup> Kayser, *Chem. Centralb.* (1888), 59, p. 261.

<sup>3</sup> Jos. K. Janks, *Spices*, New York, (1915), p. 10.

*U. S. P. Text and Comments Thereon.*

The oleoresin of pepper has been official in the *United States Pharmacopœia* since 1850, when it was recognized under the title of *Extractum Piperis Fluidum*.

1850

*Extractum Piperis Fluidum**Fluid Extract of Black Pepper*

Take of Black Pepper,<sup>1</sup> in powder,<sup>2</sup> heat, apint and a half of ether,<sup>3</sup> and a pound;

Ether,<sup>3</sup> a sufficient quantity.

Put the powder into a percolator,<sup>4</sup> evaporated,<sup>7</sup> and the deposition of piperin in crystals, has ceased. Lastly, two pints of filtered liquor are obtained.<sup>5</sup> From this distill off, by through a cloth,<sup>6</sup> and keep the liquid means of a water-bath, at a gentle portion.

1860

*Oleoresina Piperis**Oleoresin of Black Pepper**Extractum Piperis Fluidum, Pharm., 1850*

Take of Black Pepper,<sup>1</sup> in fine powder,<sup>2</sup> twelve troyounces;

Ether,<sup>3</sup> a sufficient quantity.

Put the Black Pepper into a cylindrical percolator,<sup>4</sup> press it firmly, and gradually pour ether upon it until twenty-four fluidounces of filtered liquid have passed.<sup>5</sup> Recover from this, by distillation on a water-bath, eighteen fluidounces of ether,<sup>6</sup> and expose the residue, in a capsule, until the remaining ether has evaporated,<sup>7</sup> and the deposition of piperin in crystals has ceased. Lastly, separate the oleoresin from the piperin by expression through a muslin strainer,<sup>8</sup> and keep it in a well-stopped bottle.<sup>9</sup>

1870

## Oleoresina Piperis

## Oleoresin of Black Pepper

Take of Black Pepper,<sup>1</sup> in fine powder,<sup>2</sup> twelve troyounces;  
 Ether,<sup>3</sup> a sufficient quantity.  
 Put the Black Pepper into a cylindrical percolator provided with a stop-cock, and arranged with cover and receptacle suitable for volatile liquids,<sup>4</sup> press it firmly, and gradually pour ether upon it, until twenty fluid ounces of liquid have slowly passed.<sup>5</sup>

Recover the greater part of the ether by distillation on a water-bath,<sup>6</sup> and expose the residue, in a capsule, until the remaining ether has evaporated,<sup>7</sup> and the deposition of piperin in crystals has ceased. Lastly, separate the oleoresin from the piperin by expression through a muslin strainer,<sup>8</sup> and keep it in a well-stopped bottle.<sup>9</sup>

1880

## Oleoresina Piperis

## Oleoresin of Pepper

Pepper,<sup>1</sup> in No. 60 powder,<sup>2</sup> one hundred parts ..... 100  
 Stronger Ether,<sup>3</sup> a sufficient quantity.  
 Put the pepper into a cylindrical percolator, provided with a cover and receptacle suitable for volatile liquids,<sup>4</sup> press it firmly, and gradually pour stronger ether upon it, until one hundred and fifty (150) parts of liquid have slowly passed.<sup>5</sup>

Recover the greater part of the ether by distillation on a water-bath,<sup>6</sup> and expose the residue, in a capsule, until the remaining ether has evaporated,<sup>7</sup> and the deposition of piperine, in crystals, has ceased. Lastly, separate the oleoresin from the piperine by expression through a muslin strainer.<sup>8</sup> Keep the oleoresin in a well-stopped bottle.<sup>9</sup>

1890

## Oleoresina Piperis

## Oleoresin of Pepper

Pepper,<sup>1</sup> in No. 60 powder,<sup>2</sup> five hundred grammes ..... 500 Gm.  
 Ether,<sup>3</sup> a sufficient quantity.  
 Put the pepper into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and receptacle for volatile liquids.<sup>4</sup> Press the drug firmly, and percolate slowly with ether, added in successive portions, until the drug is exhausted.<sup>5</sup> Recover the greater part of the ether

from the percolate by distillation on a water-bath,<sup>6</sup> and, having transferred the residue to a capsule, set this aside until the remaining ether has evaporated,<sup>7</sup> and the deposition of crystals of piperine has ceased. Lastly, separate the oleoresin from the piperin by expression through a muslin strainer.<sup>8</sup> Keep the oleoresin in a well-stopped bottle.<sup>9</sup>

## 1900

## Oleoresina Piperis

## Oleoresin of Pepper

Pepper,<sup>1</sup> in No. 40 powder,<sup>2</sup> *five hundred grammes* ..... 500. Gm.  
 Acetone,<sup>3</sup> *a sufficient quantity*.

Introduce the pepper into a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle for volatile liquids.<sup>4</sup> Pack the powder firmly, and percolate slowly with acetone, added in successive portions, until the pepper is exhausted.<sup>5</sup> Recover the greater part of the acetone from the percolate by

distillation on a water-bath,<sup>6</sup> and, having transferred the residue to a dish, set this aside in a warm place, until the remaining acetone has evaporated,<sup>7</sup> and the deposition of crystals of piperin has ceased. Lastly, separate the oleoresin from the piperin by straining through purified cotton.<sup>8</sup> Keep the oleoresin in a well-stoppered bottle.<sup>9</sup>

Average dose.—0.030 Gm. = 30 mil-  
 ligrammes ( $\frac{1}{2}$  grain).

## 1910

## Oleoresina Piperis

## Oleoresin of Pepper

## Oleores. Piper.

Pepper,<sup>1</sup> in No. 40 powder,<sup>2</sup> *five hundred grammes* ..... 500. Gm.  
 Ether,<sup>3</sup> *a sufficient quantity*.

Place the pepper in a cylindrical glass percolator, provided with a stop-cock, and arranged with a cover and a receptacle for volatile liquids.<sup>4</sup> Pack the powder firmly, and percolate slowly with ether, added in successive portions until the drug is exhausted.<sup>5</sup> Recover the greater part of the ether from the percolate by dis-

tillation on a water-bath,<sup>6</sup> and, having transferred the residue to a dish, set this aside in a warm place until the remaining ether has evaporated,<sup>7</sup> and the deposition of piperine has ceased. Lastly, separate the oleoresin from the piperine by straining through purified cotton.<sup>8</sup> Keep the oleoresin in a well-stopped bottle.<sup>9</sup>

Average Dose.—Metric, 0.03 Gm.—  
 Apothecaries,  $\frac{1}{2}$  grain.

1) For a description of the official drug, see page 1117 under "Drug used, its collection, preservation, etc."

2) The last two editions of the Pharmacopœia have specified that the drug be in the form of a No. 40 powder for percolation. Previous editions, with the exception of that of 1850, in which the degree of fineness was not stated, required that a fine

powder (No. 60) be used for this purpose. The coarser powder possesses the advantages of being more readily produced and of being better adapted to the rapid exhaustion of the drug.

3) The solvents which have been experimented with in the preparation of this oleoresin are alcohol, ether, acetone, benzin and petroleum ether. Of these, ether has proven to be the most satisfactory and is the solvent specified for this purpose by the present Pharmacopœia. Acetone, which was directed to be used by the Pharmacopœia of 1900, like alcohol, is unsatisfactory as the large amount of extractive matter obtained interferes with the separation of the piperine. Benzin or petroleum ether, on the other hand, dissolves piperine but slightly and, therefore, yield a product low in piperine content. See tables on page 1134.

4) For a description of percolators adapted to the use of volatile liquids, as specified for use in this connection by the Pharmacopœia, see Part I under "Apparatus used."

5) With respect to the manner of exhausting the drug, it is thought that the process of continuous extraction would be a distinct improvement over the present pharmacopœial method. The reasons for this statement have already been given in the comments of the preceding oleoresins and need not be repeated here.

6-7) As this oleoresin does not appear to undergo any noticeable changes upon exposure to the air, except to lose a small amount of volatile oil, the conditions under which the solvent is removed from the percolate are not as important as in the case of the other oleoresins. The time necessary to complete the preparation, however, can be considerably shortened if the operation is completed at the temperature of the water bath, for which reason, this procedure is thought to be justified.

8) The Pharmacopœia directs that the mixture obtained on evaporating the solvent from the percolate be allowed to stand until the deposition of the piperine is complete and that the latter then be separated from the liquid portion by straining through purified cotton. The object to be attained in allowing the piperine to deposit is not understood as it has been found in actual practice that the liquid portion does not sep-



arate as a rule, but that the whole sets to form a semi-solid mass owing to the large amount of piperine present. The means by which the separation of the piperine was accomplished in the laboratory appears to be more rational and is as follows: the mixture was heated on the water bath until the portion constituting the oleoresin was quite fluid when it was filtered through cotton with the aid of a suction pump. The piperine which deposited from the filtered oleoresin on cooling was finally separated by decantation.

9) As the oleoresin loses volatile oil on exposure to the air, it should be kept in well-stoppered bottles.

### *Yield.*

The yield of oleoresin to acetone or ether is about 4.5 to 6.5 per cent. With petroleum ether, a yield of 3.2 per cent. was obtained in the laboratory. Aside from the effect which the solvent has upon the amount of the oleoresin obtained, the temperature at which the piperin is separated is a factor to be considered. The higher the temperature at which this is accomplished, the greater the amount of piperine remaining in solution and the greater the yield of finished product, and *visa versa*.

In the tables which follow, the yield of total extract is frequently reported as oleoresin. These reports should not be confused with those pertaining to the official preparation, which consists of the liquid portion only, the precipitated piperine and other insoluble material having been removed. Data of this kind have been included here for the sake of comparison with results of a like nature obtained in the laboratory and in order to point out the erroneousness of such reports.

TABLE 123—Yield of oleoresin as reported in the literature.

Date	Observer	Yield of oleoresin to—				
		Alcohol	Acetone	Ether	Other solvents	
		Per ct.	Per ct.	Per ct.	Per cent.	
1888	Trimble .....	.....	.....	8.79	{ Benzin 2.80	Represents total yield of extractive matter. Yield of oleoresin.
1892	Beringer.....	.....	9.97 5.93	.....	.....	
	Sherrard.....	.....	.....	5.00 to 8.70	.....	Reported as yield of oleoresin <sup>(1)</sup> Pepper from the Indies. Total extract.
1903	Ballard .....	.....	.....	8.84 9.64 5.50	.....	
		.....	.....	8.70	.....	Pepper from Guadeloupe. Total extract.
		.....	.....	10 15	.....	Pepper from the coast of Dahomey. Total extract.
1913	Patch .....	.....	.....	10.04 10.87 12.88	.....	Represents total yield of extract.
"	Engelhardt.....	.....	.....	.....	{ Solvent (?) 8.20 10.60 11.00 12.50	
		.....	.....	.....	.....	Reported as yield of oleoresin. <sup>(1)</sup>

(1) Undoubtedly represents total extract.

TABLE 124—Yield of oleoresin as obtained in the laboratory.

Date	Observer	Yield of oleoresin to—				Remarks
		Alcohol	Acetone	Ether	Petrol. ether.	
		Per ct.	Per ct.	Per ct.	Per ct.	
1916	Du Mez .....	11.10	10.65	10.42	7.14	Represents total extract.
"	" .....	5.32	5.09	4.44	3.20	Represents the portion decanted and washed from the deposited piperine.

*Chemistry of the Drug and Oleoresin.**Tabulation of Constituents.*

The chemistry of black pepper has been the subject of a number of investigations<sup>1</sup> conducted during the past century. As a result of these investigations, the presence of the following substances of pharmaceutical interest has been established: volatile oil, piperine, resin, starch, coloring matter and inorganic constituents. In addition to the foregoing, the presence of fatty oil, piperidine and methyl pyrroline has been reported. The following are stated by Kayser and others<sup>2</sup> to be present in the oleoresin when prepared with ether:

Resin	Volatile Oil
Coloring Matter	Fatty Oil
Ash	Piperine

*Occurrence of Description of Individual Constituents.*

*Volatile Oil.*<sup>3</sup> According to the report of Schimmel and Company,<sup>4</sup> the volatile oil of pepper is a colorless or yellowish-green liquid, having a phellandrene-like odor. At 15°C, the specific gravity is given as 0.88 to 0.905 and the angle of rotation in a 100 millimeter tube as  $-5^{\circ} 2'$  to  $+2^{\circ} 27'$ . It is stated to be soluble in 15 parts of alcohol (90 per cent).

Early attempts to determine the composition of the oil were made by Dumas,<sup>5</sup> and Soubeiran and Capitaine.<sup>6</sup> In 1887, Eberhardt<sup>7</sup> isolated a l-terpene which he failed, however, to

<sup>1</sup> Among those who have reported more or less complete analyses of pepper the following may be mentioned: Pelletier, *Ann. de Chim. et de Phys.* (1821), 16, p. 337; Luca, *Tschenb. f. Scheidekunstl. u. Apoth.* (1822), 43, p. 81; H. Röttger, *Arch. f. Hygiene* (1886), 4, p. 183; Richardson, *U. S. Dept. of Agric. Bull. No. 13*, (1887), p. 206; Johnstone, *Chem. News* (1888), 58, p. 235; Kayser, *Chem. Centralb.* (1888), 59, p. 261; Weigle, *Apoth. Ztg.* (1893), 8, p. 468; Hebebrand, *Zeitschr. Unters. Nahr. u. Genussm.* (1896), p. 345; Winton, Ogden and Mitchell, *Ann. Rep. Conn. Exp. Sta.* (1898), p. 198; Balland, *Journ. de Pharm. et de Chim.* (1903), 157, p. 296.

<sup>2</sup> Kayser, Weigle, Balland, *l. c.*

<sup>3</sup> The description of the oil as here given is for that obtained from the fruit by distillation with steam.

<sup>4</sup> Schimmel & Co., *Semi-Ann. Rep.*, Oct. 1893, p. 34.

<sup>5</sup> *Ann. d. Chem.* (1835), 15, p. 159; *Journ. f. prakt. Chem.* (1835), 4, p. 434.

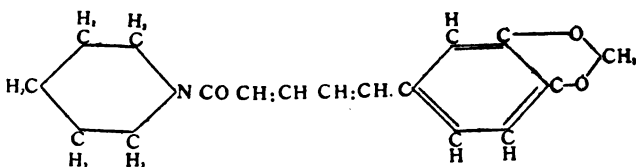
<sup>6</sup> *Journ. de Pharm. et de Chim.* (1840), 26, p. 83.

<sup>7</sup> *Arch. der Pharm.* (1887), 225, p. 515.

identify. Schimmel and Company<sup>8</sup> have reported the presence of phellandrene and cadinene.

From 0.70 to 2.2 per cent. of volatile oil has been obtained from the fruits by steam distillation.<sup>9</sup>

**Piperine.**<sup>10</sup> Piperine ( $C_{17}H_{19}NO_3$ ) was first isolated by Oersted in 1819.<sup>11</sup> It is a weak base crystallizing from alcohol in colorless, shining, four sided prisms, the melting point of which is 128 to 129°C. It is slightly soluble in boiling water, readily soluble in alcohol, ether, chloroform, benzene and volatile oils, slightly soluble in petroleum ether. When acted upon by solutions of the alkalies, it is hydrolyzed breaking down into piperidine and piperic acid. Its constitution is represented by the following structural formula:<sup>12</sup>



The quantity of piperine present in the fruit of black pepper as obtained on the market varies to a considerable extent. This variation is very probably due in greater part to natural causes, such as the age of the fruit before harvesting, climatic conditions under which grown, *et cetera*.<sup>13</sup> The yield is variously stated as being from 4.05 to 13.02 per cent.<sup>14</sup>

<sup>8</sup> *l. c.*

<sup>9</sup> A yield of 0.7 to 1.69 per cent. of volatile oil is reported by C. H. Richardson *l. c.* W. Johnstone obtained 0.98 to 1.87 per cent. *Analyst* (1889), 14, p. 41. G. Teyxeira and B. Ferrucio give the yield as 1.4 per cent. *Bull. Chim. Pharm.* (1900), 38, p. 534; *Chem. Centralb.* (1900), 71, p. 736. Schimmel & Co. (*l. c.*) report the yield as 1.3 to 2.2 per cent.

<sup>10</sup> Rochleder, *Ann. d. Chem.* (1845), 54, p. 255; Babo and Keller, *Journ. f. prakt. Chem.* (1857), 72, p. 53; Rugheimer, *Ber. d. deutsch. chem. Ges.* (1882), 15, p. 1390.

<sup>11</sup> Schweitz, *Med. Journ.* (1819), 29, p. 80; Buchner, *Repert. f. die Pharm.* (1820), 10, p. 127.

<sup>12</sup> Ladenburg and Scholtz, *Ber. d. deutsch. chem. Ges.* (1894), 27, p. 2958.

<sup>13</sup> Caseneuve and Caillot report the piperine content to be as follows: Sumatra, 8.10 per cent.; Singapore, 9.15 per cent.; Penang, 5.24 per cent. *l. c.* G. Graff gives the following percentages of ether soluble nitrogenous matter as piperine: Java, 5.85 to 9.5 per cent.; Lampong, 5.13 to 7.09 per cent.; Penang, 9.12 to 9.42 per cent.; Saigon, 6.16 per cent.; Singapore, 11.08 per cent. *Zeitschr. f. öffentl. Chem.* (1908), 14, p. 425.

<sup>14</sup> W. Johnstone obtained 5.21 to 13.03 per cent of piperine from nine samples of black pepper, *l. c.*

C. Hensch gives the yield as 4.05 to 9.38 per cent. *Analyst* (1886), 11, p. 186.

F. Stevenson reports the presence of 7.14 per cent. of piperine. *Ibid.* 12, p. 144.

**Resin.** The presence of 1.25 to 2.08 per cent. of resin in black pepper has been reported.<sup>15</sup> Buchheim,<sup>16</sup> the only investigator who appears to have attempted to isolate the same in sufficient purity to determine its composition, states that it is a condensation product of piperidine with an acid, to which he gives the name *Chavicinsäure*. He assigns the name *Chavicin* to this compound, and describes it as a yellowish-brown mass soluble in alcohol, ether, petroleum ether and the other common solvents.

**Coloring Matter.** The green coloring matter in pepper is stated to be chlorophyll.<sup>17</sup> The brown coloring matter observed in the ethereal or alcoholic extracts has not been identified.

**Fatty Oil.**<sup>18</sup> The presence of a fatty oil in black pepper must be considered doubtful at the present time. Hirsch<sup>19</sup> states that a microscopical examination of the fruit revealed the presence of a fatty oil in the endosperm. Kayser,<sup>20</sup> Weigle,<sup>21</sup> and others mention fatty oil as one of the constituents. None of these investigators, however, appear to have isolated the oil in a pure state or to have described it in detail. Ditzler,<sup>22</sup> who made this matter the subject of a special investigation, concluded that glycerides were absent. Likewise, Gerock<sup>23</sup> could obtain no fat from white pepper.

**Piperidine.**<sup>24</sup> Piperidine has been named as a constituent of black pepper by Johnstone,<sup>25</sup> who found the average content of nine samples to be 0.56 per cent. Kayser<sup>26</sup> disputes the findings of Johnstone and states that the base obtained by distillation is ammonia.

<sup>15</sup> Teyxeira and Ferrucio give the resin content as 1.25 per cent., F. Stevenson as 1.44 per cent. l. c.

F. Blyth reports the presence of 1.7 to 2.08 per cent. *Foods, Their Composition and Analysis* (1903), p. 496.

<sup>16</sup> Buchner's n. Repert. f. Pharm. (1876), 25 p. 335; Pharm. Journ. 1876, 36, p. 315.

<sup>17</sup> Arthur Meyer, *Das Chlorophyllkorn*, Leipzig (1883), p. 2.

<sup>18</sup> In the literature on food chemistry, the non-volatile ether extract is usually spoken of as fat or fatty oil. See Winton, Ogden and Mitchell, l. c.

<sup>19</sup> Flueckiger, *Pharmakognosie des Pflanzenreiches* (1891), p. 914.

<sup>20</sup> l. c.

<sup>21</sup> l. c.

<sup>22</sup> Arch. d. Pharm. (1886), 224, p. 103.

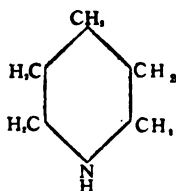
<sup>23</sup> *Ibid.*

<sup>24</sup> As piperidine is one of the products obtained when piperine is hydrolysed, it is quite probable that it is not a normal constituent of the fruit but is formed when the powdered material is subjected to distillation.

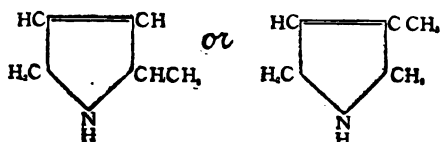
<sup>25</sup> l. c.

<sup>26</sup> l. c.

Piperidine is a colorless limpid liquid having a specific gravity of 0.8591 at 25°C, and boiling at 106.3°C.<sup>27</sup> It is stated to have an odor resembling both, that of ammonia and pepper. It is a powerful base behaving generally like ammonia in its action on the metallic bases. It is soluble in all proportions in alcohol or water. It has the following structural formula.<sup>28</sup>



*Methyl-Pyrroline.* Pictet and Court<sup>20</sup> report the occurrence of 0.01 per cent of methyl-pyrroline in black pepper obtained from Singapore. The exact constitution has not been determined, but the authors are of the opinion that it is a C-methyl pyrroline represented by one of the following formulas:



*Ash.* The basic elements, K, Na, Mg, Ca, Fe and Mn, combined with the acids, HCl, H<sub>3</sub>PO<sub>4</sub>, H<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>SiO<sub>3</sub>, are the components of the ash of black pepper as determined by Rottger<sup>29</sup> and others.<sup>31</sup>

The average ash content of black pepper is stated by Blyth<sup>32</sup>

<sup>27</sup> Perkin, Chem. Soc. Journ. (1889), 55, p. 699.

<sup>28</sup> Hofmann, Ber. der. deutsch. chem. Ges. (1879), 12, p. 985; Koenigs, *Ibid.*, p. 2341; Ladenburg, *Ibid.* (1885), 18, pp. 2956 and 3100.

<sup>29</sup> Pictet states that he was able to isolate pyrrolidine and N-methyl pyrroline from various leaves by steam distillation after treatment with sodium carbonate. He is of the opinion that the methyl pyrrolines undergo rearrangement forming pyridine and quinoline rings, thus giving rise to the more complex alkaloids. Arch. Sci. Phys. Nat. (1905), 19, p. 329; Ber. d. deutsch. chem. Ges. (1907), 40, p. 3771.

<sup>30</sup> Arch. Hyg. (1886), 4, p. 183. "

<sup>31</sup> Blyth, Chem. News (1874), 30, p. 170.

<sup>32</sup> *Ibid.*

to be 4.845 per cent. As high as 8.99 per cent. has been reported.<sup>22</sup>

### *Constituents of Therapeutic Importance*

The oleoresin of pepper is said to be used chiefly in the South, where it is administered with quinine in the treatment of "intermittent fever." Its value in this connection is accounted for by the presence of piperine which has been shown to be an active antiperiodic.<sup>1</sup> Piperidine and methyl pyrrolone, if present, would impart similar properties,<sup>2</sup> while the composition of the contained volatile oil would indicate a carminative action.

### *Physical Properties*

**Color:** The color of the oleoresin, when the latter was spread out in a thin layer on a white porcelain surface, was observed to be a greenish-brown, closely resembling that of the oleoresin of cubeb when prepared from the ripe fruits. The so-called oil of black pepper, sometimes sold as a substitute for the official oleoresin, is stated to be considerably darker in color due to the removal of the greater part of the volatile oil.

**Odor:** The odor, while slight, resembles that of ground pepper.

**Taste:** The taste is sharp and spicy, the sharpness becoming more noticeable after the oleoresin has been retained in the mouth for a short time.

**Consistence:** The oleoresin is a thick, sticky liquid which can only be poured with difficulty. The fluidity is greatly increased by heating the preparation on a water bath.

**Solubility:** The oleoresin is completely soluble in alcohol, ether, acetone, chloroform, carbon disulphide and glacial acetic acid. It is only partially soluble in petroleum ether and is insoluble in water.

**Specific gravity:** The specific gravity of the oleoresin is fairly constant, only, when similar conditions with respect to

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<sup>22</sup> Heish reports the ash content of 8 samples of black pepper to be from 4.35 to 8.99 per cent. *Analyst* (1886), 11, p. 186. Others who have reported on the ash content of pepper are Bergman, *Zeitschr. f. Analyt. Chem.* (1882), 21, p. 535, and von Raumer, *Zeitschr. angew. Chem.* (1893), p. 453.

<sup>1</sup> Wood, *Therapeutics, Principles and Practice*, (1908), p. 482.

<sup>2</sup> Tunncliffe and Rosenheim, *Centralbl. f. Physiol.* (1902), 16, p. 93.

temperature have been observed during the separation of the precipitated piperine. A comparatively slight difference in temperature causes a considerable variation in the amount of the latter constituent retained in solution, which results in a corresponding variation in the specific gravity of the finished product. This effect is further noticed in connection with the menstruum employed in extracting the drug, e. g. petroleum ether which is a poor solvent for piperine yields an oleoresin relatively low in specific gravity. With respect to the commercial samples examined, a low specific gravity was, in one instance, found to be due to the presence of unevaporated solvent. The tables which follow show the specific gravity of the samples examined in the laboratory.

TABLE 125—*Specific gravities of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Specific gravity
1.....	1916	DuMez.....	Alcohol.....	At 25° C 1.069
2.....	"	" .....	Acetone .....	1.083
3.....	"	" .....	Ether .....	1.056
4.....	"	" .....	Petrol. ether .....	0.981

TABLE 126—*Specific gravities of commercial oleoresins.*

Sample No.	Date	Observer	Source	Specific gravity
1.....	1916	DuMez.....	Squibb & Sons.....	At 25° C 0.985 <sup>1</sup>
2.....	"	" .....	Sharp & Dohme .....	1.061

<sup>1</sup> The odor of ether was very noticeable.

*Refractive index:* The refractive index of this preparation as observed in the laboratory was not constant, varying from 1.521 to 1.696. From an inspection of the first of the tables which follow, it would appear that this variation was a result of the influence of the solvent employed in extracting the drug. While the solvent undoubtedly exerts an influence in this connection, it does so indirectly, that is, through its effect on the piperine content.<sup>1</sup> The latter, however, is also influenced by

<sup>1</sup> See discussions under "Piperine content" and "Yield of oleoresin," respectively.



the temperature at which the preparation is finished—the temperature at which the liquid oily portion, which constitutes the official oleoresin, is separated from the deposited material, including the excess of piperine. In the case of commercial samples, the piperine content and, therefore, the refractive index may also be affected by the presence of unevaporated solvent. The results obtained in the laboratory in the determination of this property are given in the tables which follow.

TABLE 127—*Refractive indices of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Refractive index
				At 25° C
1.....	1916	DuMez.....	Alcohol.....	1.559
2.....	"	" .....	Acetone .....	1.696
3.....	"	" .....	Ether.....	1.562
4.....	"	" .....	Petrol, ether.....	1.521

TABLE 128—*Refractive indices of commercial oleoresins.*

Sample No.	Date	Observer	Source	Refractive index
				At 25° C
1.....	1916	DuMez.....	Squibb & Sons.....	1.501(a)
2.....	"	" .....	Sharp & Dohme.....	1.560

(a) Contained ether.

### *Chemical Properties.*

*Loss in weight on heating:* A loss in weight varying from 9.49 to 11.52 per cent. was obtained for the laboratory preparations, when heated at 110°C, showing that the nature of the solvent employed in extracting the drug has but little influence on this property. With respect to the commercial samples examined, the loss was much greater, being as high as 32.64 per cent. in one case. The comparatively great loss in the latter instance was due to the presence of unevaporated solvent (ether.) The results obtained in the determination of this constant in the laboratory follow.

TABLE 129—Laboratory preparations—loss in weight on heating.

Sample No.	Date	Observer	Solvent	Per cent. of loss on heating
1.....	1916	DuMez.....	Alcohol.....	At 110° C 10.34
2.....	"	" .....	Acetone.....	11.52
3.....	"	" .....	Ether.....	10.91
4.....	"	" .....	Petrol, ether .....	9.49

TABLE 130—Commercial oleoresins—loss in weight on heating.

Sample No.	Date	Observer	Source	Per cent. of loss on heating
1.....	1916	DuMez.....	Sharp & Dohme.....	At 110° C 17.52
2.....	"	" .....	Squibb & Sons.....	52.64 <sup>1</sup>

<sup>1</sup> Unevaporated solvent (ether) was present.

*Ash content:* The ash determinations made on the oleoresins prepared in the laboratory show that the solvent employed in their preparation is the chief factor influencing the results obtained. The official product, in the making of which ether was the solvent used, yielded 0.11 per cent. of ash, which was about the percentage yield obtained for one of the commercial samples examined. The other commercial oleoresin gave 0.29 per cent. of ash indicating the use of acetone in its preparation. Both samples contained copper, apparently, however, in quantities too small to noticeably affect the weight of the ash. The results of the determinations made in the laboratory follow:

TABLE 131—Ash contents of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Per cent of ash
1.....	1916	DuMez.....	Alcohol.....	0.45
2.....	"	" .....	Acetone .....	0.32
3.....	"	" .....	Ether.....	0.11
4.....	"	" .....	Petrol, ether .....	0.05

TABLE 132—*Ash content of commercial oleoresins.*

Sample No.	Date	Observer	Source	Per cent. of ash	Foreign constituents
1.....	1916	DuMez.....	Squibb & Sons...	0.12 (a)	Copper
2.....		.....	Sharp & Dohme..	0.29	

<sup>1</sup> Contained ether.

*Acid number:* The acid number of the oleoresin when prepared with alcohol, acetone or ether was found to be about 19. In the case of the two commercial samples examined, however, the values obtained differed to a considerable extent, being 19.2 in one instance and 27.5 in the other. As the preparation represented by the first number contained considerable unevaporated solvent, this difference can be accounted for in part. The high values obtained for the commercial samples are thought to be due to their relatively low piperine content or to a partial decomposition of the resin. The values obtained for this constant in the laboratory follow.

TABLE 133—*Acid numbers of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Acid number
1	1916	DuMez.....	Alcohol .....	19.2
2	"	" .....	Acetone .....	19.0
3	"	" .....	Ether .....	18.9
4	"	" .....	Petrol.-ether.....	15.1

TABLE 134—*Acid numbers of commercial oleoresins.*

Sample No.	Date	Observer	Source	Acid number
1	1916	DuMez.....	Squibb & Sons.....	19.2 (a)
2	"	.....	Sharp & Dohme.....	27.5

(a) Contained ether.

*Saponification value:* As will be observed in an inspection of the first of the tables which follow, the saponification value of the oleoresin varies with the solvent employed in its preparation. This appears to be due principally to the effect which the nature of the solvent has upon the piperine content of the

finished product, e. g. the piperine content of the preparation made with acetone was found to be 54.36 per cent and the saponification value 88.6, while the oleoresin when prepared with petroleum ether, contained only 15.06 per cent. of piperine and gave a saponification value of 109.5. Other influences, besides the nature of the solvent, affecting the piperine content may likewise produce a variation in the saponification value, e. g. the temperature at which the preparation is made and the presence of unevaporated solvent in the finished product. The latter may also have a direct influence. The saponification values as found for the oleoresins examined in the laboratory are given in the following tables.

TABLE 135—*Saponification values of oleoresins prepared in the laboratory.*

Sample No.	Date	Observer	Solvent	Saponification value
1.....	1916	DuMez.....	Alcohol.....	63.7
2.....	"	".....	Acetone.....	74.9
3.....	"	".....	Ether.....	83.5
4.....	"	".....	Petrol, ether.....	86.8

TABLE 136—*Saponification values of commercial oleoresins.*

Sample No.	Date	Observer	Source	Saponification value
1.....	1916	DuMez.....	Sharp & Dohme.....	66.3
2.....	"	".....	Squibb & Sons.....	73.7 (a)

(a) Contained ether.

*Iodine value:* Iodine values ranging from 88.6 to 95.4 were obtained for this oleoresin when acetone, alcohol or ether were the solvents employed in its preparation. This variation is due to the difference in the piperine content of these oleoresins as a result of operating under different conditions of temperature when preparing the same, as well as to the nature of the solvent. In addition to these influences, the presence of unevaporated solvent must also be taken into consideration in the case of the commercial samples, as is indicated by the values given in the following tables.

TABLE 137—Iodine values of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Iodine value
1	1916	DuMez. ....	Alcohol.....	90.0
2	"	" .....	Acetone .....	88.6
3	"	" .....	Ether .....	95.4
4	"	" .....	Petrol.-ether.....	109.5

TABLE 138—Iodine values of commercial oleoresins.

Sample No.	Date	Observer	Source	Iodine value
1	1916	DuMez.....	Sharp & Dohme.....	83.7
2	"	" .....	Squibb & Sons.....	89.9 (a)

(a) Contained ether.

*Special Quantitative Tests.*

At the present time, there does not appear to be a method in use for the evaluation of this oleoresin. As its therapeutic properties are due, in greater part at least, to its piperine content,<sup>1</sup> a quantitative method for the estimation of this constituent appears to offer the best means of determining its quality.

*Method for the Estimation of the Piperine Content.*

In the laboratory, the amount of piperine present was computed from the nitrogen content of the oleoresin, the latter being determined by the Gunning-Arnold<sup>2</sup> method. The results obtained are given in the following tables:

TABLE 139—Piperine content of oleoresins prepared in the laboratory.

Sample No.	Date	Observer	Solvent	Piperine content
1.....	1916	DuMez.....	Alcohol.....	Per cent. 47.0
2.....	"	" .....	Acetone .....	54.3
3.....	"	" .....	Ether .....	51.3
4.....	"	" .....	Petrol, ether .....	15.1

<sup>1</sup> See under "Constituents of therapeutic importance."<sup>2</sup> Bull. No. 107, Bur. of Chem. (1912), p. 162.

TABLE 140—*Piperine content of commercial samples.*

Sample No.	Date	Observer	Source	Piperine content
1.....	1916	DuMez.....	Sharp & Dohme.....	Per cent. 27.3
2.....		.....	Squibb & Sons.....	33.8

The laboratory samples were prepared and tested during the warm months of summer, which accounts for the high piperine content. A very considerable amount of the latter precipitated out during the colder months which followed. It is, therefore, thought that the results obtained in the case of the commercial products are the more typical.

#### *Adulterations.*

Copper was found to be present in all of the commercial samples examined. See under "Ash content."

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Planche

1823

Von den pharmaceutischen Zubereitungen des Lupulins.

Mag. f. Pharm., 1, p. 183. [Trommsdorff's n. Journ. d. Pharm., 7, p. 345.]

A method for preparing the alcoholic tincture of lupulin is given. It is further stated that an extract similar in all respects to the resin said to have been isolated by Ives results when the alcohol is removed from the tincture by evaporation.

Geiger, Ph. L.

1824

Versuche über die chemische Zusammensetzung der Wurzel des maennlichen Farrenkrauts, *Polypodium (Aspidium, Nephrodium) Filix Mas*.

Mag. f. Pharm., 7, p. 38.

The article is a review of Morin's analysis of the rhizome of male fern with a note pointing out that Morin was not the first investigator to make such an analysis, but that Gebhardt had already published an analysis of the same in 1821 in an inaugural dissertation delivered at Kiel. Gebhardt is stated to have used ether for extracting the "oil."

Morin

1824

Sur la composition chimique de la racine de fougère mâle, *Polypodium filix mas* Linn.

Journ. de Pharm. et de Chim., 10, p. 223. [Mag. f. Pharm., 7, p. 38.]

In making a chemical examination of the male fern rhizomes, the author used the method of selective solvents. Upon extracting with ether, as the first solvent, and subsequently evaporating of the ether, a thick green fatty oil was obtained. The author considers this fatty substance the active principle.

Meli

1825

Neue Erfahrungen und Beobachtungen ueber die Art, das Alkaloid und das scharfe Oel des Pfeffers zu gewinnen.

Trommsdorff's n. J. d. Pharm., 11, p. 174. [Bull. de scien. math., phys. et chim., 1825, p. 191.]

It is stated that more than an ounce and a half of piperine and about four ounces of a sharp tasting oil were obtained from three pounds of black pepper by extraction with alcohol.

Peschier, Ch.

1825

Oel des maennlichen Farrenkrauts (*Aspidium Filix Mas*), ein sehr vorzuegliches und sicheres Mittel gegen den Bandwurm.

Biblioth. univers., Nov. 1825, p. 205. [Mag. f. Pharm., 13, p. 188.]

The so called oil, *Huile de Fougère Mâle*, is directed to be prepared by extracting the powdered male fern rhizomes with ether and subsequently removing the ether by warming gently.

Buchner, A.

1826

Extractum Filicis maris resinorum.

Repert f. d. Pharm., 23, p. 433.

The preparation of this extract by means of alcohol instead of ether is recommended. The product thus obtained is spoken of as an *Extractum resinorum*. The *Huile de Fougère* of Peschier is spoken of as the *harthaltiges Oel*. A chemical analysis of the extract is also given.

von Esenbeck, Nees

1826

Farrenkrautwurzelextrakt.

Arch. d. Pharm., 19, p. 153.

The extract is reported to have been prepared by the process of maceration, ether being the solvent employed. Four ounces of rhizomes gathered in August gave 108 grains of extract.

1827

Verhandlungen des pharmaceutischen Vereins in Wuerttemberg. Repert. f. d. Pharm., 26, p. 441.

Zeller is stated to have prepared the *Extractum radice Filicis maris resinosum* according to the method suggested by Buchner; extraction with alcohol. The extract obtained in this manner from rhizomes gathered in September amounted to 30 per cent. of the air dried drug.

Batso, V.

1827

Dissertatio inaugur. chemica de Aspidio filice mara Quam cons. et auctor. praes et direct. etc., pro summis in scient. et arte chemica honor. et doct. laurrite cappess. in univers. vindobon. publ. erudit, disq. submittit Valentinus Batso, N. H. Debreczino Bibariensis p. 37, 8. Vindobonae, typis Antonii Pichler. 1826. [Trommsdorff's n. Journ. d. Pharm., 14, 2, p. 249.]

In addition to oil, resin and fatty wax, the author finds a free acid and an alkaloid in the ethereal extract of male fern. He calls the acid *Acidum filiceum* and the alkaloid *Filicina*. He attributes the activity of the extract to these two substances.

Brandes, R.

1827

Ueber das Extractum oleo-resinosum Filicis.  
Arch. d. Pharm., 21, p. 253.

The physical properties of the extracts obtained by extracting male fern rhizome with ether and with *Liquor anodynus*, respectively, are described.

Buchner, A.

1827

Zur medicinischen und chemischen Geschichte der Filix mas.  
Repert. f. d. Pharm., 27, p. 337.

The author speaks of the ethereal extract of male fern as the *Extractum oleoso-resinosum Filicis maris*. It is stated to contain a volatile oil, a green fatty oil, a fatty wax, a brown resin and a volatile acid (probably acetic acid.)

Van Dyk

1827

Ueber das Oleum Filicis maris.  
Arch. d. Pharm., 22, p. 141.

Two ounces of powdered male fern rhizome gave 70 grains of ethereal extract, while 8 ounces of the rhizome yielded 3 ounces of extractive matter



to alcohol. The extract prepared with ether is stated to be dark olive-green in color and of the consistence of honey, that prepared with alcohol greenish-brown in color and much thicker.

Geiger, Ph. L.

1827

Analytische Versuche mit der Wurzel des maennlichen Farrenkrauts und Darstellung des Oels (*Ol. Filicis Maris*) aus derselben.

Mag. f. Pharm., 17, p. 78.

The ethereal extract when prepared from green rhizome, by extraction with ether in a *Realsche Presse* is said to be a yellowish-green oily substance.

An analysis of this extract showed the presence of 30 per cent. of resinous material soluble in alcohol, 50 per cent. of a fixed oil and a considerable amount of volatile substances.

Tilloy

1827

Bereitungsart des Oels des maennlichen Farrenkrauts.

Journ. de Chim. med., 3, p. 154. [Geiger's Mag. f. Pharm., 18, p. 157.]

The so-called oil of male fern is directed to be prepared by extracting the rhizome with alcohol. The alcoholic liquor thus obtained is treated with lead subacetate, filtered, and the solvent removed by distillation. The resulting oil is further purified by dissolving in ether and evaporating.

Dublanc, H.

1828

Extrait oléorésineux de Cubebe.

Journ. de Pharm. et de Chim., 14, p. 41.

The author's method for preparing the oleoresinous extract consists in distilling off the volatile oil with water, exhausting the dried marc with alcohol, evaporating off the alcohol, and mixing the residue so obtained with the volatile oil.

Meylink

1828

Ueber das Extractum oleo resinum Filicis.

Arch. d. Pharm., 25, p. 243.

Two ounces of the powdered male fern rhizome are reported to have yielded 58 grains of a dark green, oily extract to ether.

Oberdoerffer

1826

Ueber die Darstellung des Cubeben Extracts.

Arch. d. Apoth. Ver., 24, p. 178.

In the method of preparation, the oil is first obtained by steam distillation, the marc remaining in the still, after drying, is then extracted with

alcohol. The residue remaining after removing the alcohol by evaporation is mixed with the volatile oil, this mixture constituting the so-called extract.

Peschier, Ch.

1828

Ueber mehrere schon frueher erschienene Analysen der Farrenkrautwurzel (*Aspidium filix mas L.*) und ueber die Gewinnung seines harzigen Oels.

Trommsdorff's n. Journ. d. Pharm., 17, p. 5.

The vermifuge properties of male fern are said to be due to its oléo-résine (*oelharz*) content. This the author prepares by extracting the drug with ether and subsequently evaporating the solvent. (p. 8.) It is further stated that this oleoresine remains perfectly homogenous after months if prepared from freshly gathered rhizomes, but deposits a white granular substance when old rhizomes are used (p. 9.)

According to the author's analysis the oleoresine consists of a volatile aromatic oil, a fatty oil, resin, stearin, green and red coloring materials, acetic and gallic acids.

Winkler, F. L.

1828

Einige Worte ueber die Bereitung des Ol. Filic. Maris.

Geiger's Mag. f. Pharm., 22, p. 48.

The "oil" extracted with ether is said to be a mixture of oil, resin and oxidized tannin. Twelve ounces of rhizomes gathered in February yielded 15 drachms of extract. Two drachms of this extract yielded 43 grains of fatty oil.

Allard

1829

Note sur l'huile de fougère.

Journ. de Pharm. et de Chim., 21, p. 292.

The powdered rhizome of the male fern is directed to be extracted with alcohol and the alcoholic extract after evaporating off the solvent, washed with water. The extract is then further purified by solution in ether and subsequent evaporation.

Carpenter, G. W.

1829

Observations and Experiments on Peruvian Bark.

Silliman's Am. Journ., 16, p. 28. [Buchner's Rept f. d. Pharm., 34, p. 446.]

In the discussion of the therapeutic uses of the various constituents of Peruvian bark, it is stated that Dr. Chapman of Philadelphia prescribed piperin and oil of pepper in combination with quinine. The oil of pepper is said to be the more active therapeutically, one drop of oil being equivalent to three grains of piperin (p. 39.)

Haendess

1829

Ueber Ol. filicis maris.

Arch. d. Pharm., 28, p. 212.

Four ounces of powdered male fern rhizomes gave 170 grains of ethereal extract. Upon treating this ethereal extract with alcohol, 20 grains were dissolved leaving a residue of 150 grains. The extract first obtained was of a brownish color, after treating with alcohol it assumed a beautiful green color.

Voget

1829

Notiz ueber Ol. filicis maris.

Arch. d. Pharm., 30, p. 104.

According to the author's method of preparing the *Oleum filicis maris*, the powdered male fern rhizome is first extracted with water. After drying the drug is then extracted with ether. Twenty-eight grains of a brownish-green extract were obtained from 9 drachms of the marc.

Schuppmann

1830

Extractum resinosum Seminis Cynae.

Buchner's Repert. f. d. Pharm., 35, p. 430.

The extract is directed to be prepared by macerating 4 ounces of the coarsely powdered seed with 16 ounces of ether for 3 or 4 days, decanting the liquid portion and evaporating to remove the solvent.

Béral

1834

Du principe du gingembre, et formules de plusieurs composés pharmaceutiques dont il est la base médicamenteuse.

Journ. de Chim. med., Pharm. et Tox., 10, p. 289.

The product obtained by extracting ginger with ether is designated *Piperoïde du Gingembre*. It is directed to be prepared by extracting in a percolator 4 ounces of ginger with 6 ounces of ether, the rate of flow being so regulated that the operation will consume not less than 2 hours. It is stated that 5 scruples of *piperoïde* were obtained in this manner, and that 6 scruples can be obtained if the residual ether is forced out by subsequent percolation with alcohol (40°). The *piperoïde* is reported to be soluble in ether, anhydrous alcohol and oils.

1838

Extrait Oléo-Résineux de Cubebe,

Journ. de Chim. med., Pharm. et Tox., 14, p. 366.

It is stated that Hausman prepared the oleoresinous extract of cubebs by macerating the powdered drug with ether (625 grams of ether to 250 grams of drug), then decanting and evaporating the ethereal solution to remove the solvent.

Hornung 1844

Pharmaceutisch-Chemische Mittheilungen.

Arch. d. Pharm., 89, p. 34.

Three ounces of fresh, powdered rhizomes of male fern, treated with 3 ounces of ether in a *Verdraengungsapparat*, are reported to have yielded 2 drachms of extract.

Luck, E. 1845

Ueber einige Bestandtheile der Radicis Filicis.

Ann. d. Chem., 54, p. 119.

Upon standing, the ethereal extract deposits a granular substance which can be obtained quite pure by pouring off the supernatant oily layer and washing the deposit rapidly with ether. The washed precipitate, dissolved in ether, crystallizes, upon evaporation, in rhombic leaflets, m. p. 160°C, insoluble in alcohol or water. The crystals were not obtained in a sufficient degree of purity to determine their chemical constitution.

Procter, Wm., Jr. 1846

On the Ethereal Extract of Cubebs.

Am. Journ. Pharm., 18, p. 167. [Pharm. Journ., 6, p. 319.]

At Dr. Goddard's request, Procter prepared a "true oleoresin" of cubebs by extracting the drug with ether. This method is regarded by him as a great improvement over the method of Soubeiran.

Bell 1846

Oleoresinous Extract of Cubebs.

Pharm. Journ., 6, p. 319.

The report includes a reprint of Procter's paper on the ethereal extract of cubebs and remarks by Ure, at whose request the preparation was made and by whom it is stated to have been used with success. A yield of 15 to 20 per cent. of oleoresin was obtained.

Procter, Wm., Jr. 1849

Remarks on oleoresinous ethereal extracts, their preparation and the advantages they offer to the medical practitioner.

Am. Journ. Pharm., 21, p. 114.

A method for the preparation of the following ethereal extracts is given: capsicum, chenopodium, semen contra, ginger, cardamom and pellitory. (p. 116.) Several forms of apparatus, including a tin percolator, Mohr's apparatus for extracting with ether and Gilbertson's displacement apparatus are also described as being useful in this connection.

Bock, H.

1851

Analyse der Wurzel und des Wedels von *Filix mas*.

Arch. d. Pharm., 115, p. 257. [Am. Journ. Pharm., 24, p. 61.]

The powdered rhizomes were extracted with ether, specific gravity 0.720. By this means, 2000 grains of the powder are reported to have yielded 257.4 grains of an oily extract which was found to be composed of volatile oil, tannic acid, resin, fatty oil stearin and chlorophyll.

The author recommends preparing the oleoresin from fresh rhizomes as he states that the greater part of the volatile oil is lost upon drying and the fatty oil tends to become rancid.

Lucke, E.

1851

Ueber einige Bestandtheile der Wurzel von *Aspidium Filix mas*.

Jahrb. f. prakt. Pharm., 22, p. 130. [Arch. d. Pharm., 119, p. 178; Journ. de Pharm. et de Chim., 54, p. 476.]

A crystalline substance resembling the *Filicin* obtained by Trommsdorff eight years previous was isolated from the ethereal extract. The author calls it *Filixsäure* and assigns it the formula  $C_{22}H_{18}O_6$ . It is further stated that extracts prepared with ether contain no tannic acid or sugar, but filix acid, pteritannic acid and fatty oil are present. Upon being saponified, the oil yielded *Filixolinsäure* ( $C_{24}H_{34}O_4 + H_2O$ ) and *Filiosmylsäure*.

Von der Marck, W.

1852

Ueber Verfaelschung der Radicis *Filicis maris*.

Arch. d. Pharm., 120, p. 87.

The botanical characteristics of other than the official species are enumerated and the manner in which they differ from those of male fern pointed out.

With respect to the male fern rhizomes, the author gives the following information: rhizomes gathered in September are the most active as they contain the greatest amount of oil. In the preparation of the extract, only that portion of the rhizome having borne fronds in the year collected, should be taken. The following results were obtained using different parts of the rhizome:

- 1.) Extract from portion of rhizome which had borne fronds the previous year. Yield 7.8% of a brownish-green extract.
- 2.) Extract from portion bearing fronds during year collected. Yield 8.2% of a beautiful green extract.
- 3.) Extract from portion which will develop fronds the coming year. Yield, 8.5% of a beautiful green extract.

- Schuck, F. 1852  
Ueber Cubebin  
Buchner's n. Repert. f. d. Pharm., 1, p. 213. [Jahresb. d. Pharm., 12, p. 34.]

Cubebin is stated to be slowly deposited from the ethereal extract of cubeb upon standing. The extract prepared from 17 ounces of cubeb gave 15 grains of cubebin.

- Bakes, W. C. 1853  
Extract of Capsicum.  
Am. Journ. Pharm., 25, p. 513.

The extract was prepared at the request of a physician. Dilute alcohol was employed for exhausting the drug. Eight ounces of Capsicum yielded two ounces of extract.

It is stated that a simple ointment which acts as a rubiafacient in 20 minutes may be prepared by mixing one drachm of this extract with 1 ounce of simple cerate.

- Livermore 1853  
Extract of Lupulin.  
Am. Journ. Pharm., 25, p. 294.

The extract is directed to be prepared by maceration, using alcohol as the solvent. Sixty-six per cent. of extractive matter was obtained by this treatment.

- Garot and Schaeuffele 1857  
Rapport sur le produit oléo-résineux de cubebe obtenu a l'aide du sulfure de carbone.  
Journ. de Pharm. et de Chim., 65, p. 368.

The article is on the experimental preparation of the oleoresin of cubebs with carbon disulphide. This solvent is proven to be worthless for this purpose on account of the large amount necessary for extracting the drug and on account of the difficulty in removing it by evaporation.

- Landerer, X.  
Ueber Cubebinum.  
Arch. d. Pharm., 139, p. 302.

The so-called cubebin was obtained in the preparation of *Extractum Cubebarum oleoso-resinosum*, for which a mixture of ether and alcohol was used. Upon standing in a cool place, needle-like crystals adhering in groups were noticed. These crystals were soluble in warm alcohol and gave a carmine red color with sulphuric acid.

Procter, Wm., Jr.

1859

Formulae for the fluid extracts in reference to their more general adoption in the next pharmacopœia.

Proc. A. Ph. A., 8, p. 265. [Am. Journ. Pharm., 31, p. 548.]

It is suggested that the preparations made by extracting drugs with ether be designated as *Oleoresinae* in the next pharmacopœia. Methods for preparing the following oleoresins are described: "*Oleoresina Cardamoni, Oleoresina Carophylli, Oleoresina Cubebae, Oleoresina Filicis maris, Oleoresina Lupulinae, Oleoresina Piperis Nigri, Oleoresina Pyrethri, Oleoresina Sabinae, Oleoresina xanthoxyli* and *Oleoresina Zingiberis*."

Girtle

1863

Extractum Cubebarum oleoresinosum.

Pharm. Centralh., 3, p. 608. [Canstatt's Jahresber., 23, p. 178.]

The preparation is an aqueous-alcoholic-etheral extract with which the volatile oil, previously obtained by distillation, has been incorporated. It is said to represent the therapeutic properties of the entire drug. It is also stated that this preparation is not identical with the *Extr. Cub. oleosoresinosum* of Landerer (1857.)

Parrish, E.

1864

On Capsicum.

Proc. A. Ph. A., 12, p. 262. [Jahresb. f. Pharm. 1, p. 68.]

In discussing the constituents of capsicum, Parrish refers to the ethereal extract as the oleoresin.

Bernatzik, W.

1865

Chemische Untersuchung der Cubeben mit besonderer Beruecksichtigung der Wirkungsweise ihrer wesentlichen Bestandtheile.

Buchner's Repert. f. d. Pharm., 14, p. 97. [Arch. Pharm., 179, p. 123.]

The article is a comprehensive discussion of the constituents of cubebs and their physiological and therapeutic action.

Based on the results of clinical experiments, it was concluded that the desired therapeutic principle is the resinous constituent and that the volatile oil, cubeb camphor and cubebin are practically of no therapeutic value. A method for preparing the *Extractum Cubebarum resinosum*, in which cubebs freed from the volatile oil are extracted with alcohol, is given (p. 139.)

Procter, Wm., Jr.

1866

Note on Oleoresina Cubebae.

Am. Journ. Pharm., 38, p. 210. [Pharm. Journ., 25, p. 620.]

The author reports the results obtained in the extraction of cubebs with ether, alcohol and benzine. The yield of oleoresin obtained was as follows: ether, 21.9 per cent., alcohol, 27 per cent., benzine, 16.5 per cent. (p. 212). The use of benzine in the preparation of this oleoresin is not recommended as it does not extract the cubebin completely.

Rittenhouse, H. N.

1866

On Substitutes for Ether and Alcohol in the Preparation of the Official Oleoresins.

Proc. A. Ph. A., 14, p. 208. [Am. Journ. Pharm., 38, p. 24.]

The feasibility of displacing the ether remaining in the exhausted drug with benzine, glycerine or water is discussed. From experiments conducted along this line, it was concluded that benzine would be the most preferable for this purpose. A working formula in which benzine is used to this end is described. Cubebs and ginger were the drugs employed in the experiments.

Paul, C.

1867

Sur l'extract oléorésineux de cubebe.

Journ. de Pharm., et de Chim., 84, p. 197.

The extract is directed to be prepared by treating the powdered drug successively with water, alcohol and ether. The extract so prepared is said to contain all of the medicinal principles of the original drug.

Pile

1867

On the preparation of Oleoresins with benzine.

Proc. A. Ph. A., 15, p. 94.

One pound of cubebs percolated with 2 pounds of light benzine, specific gravity 86°, Beaumé, is stated to have yielded a trifle over 5 per cent. of oleoresin of a pale ash color.

It is further stated that neither benzine nor ether completely exhaust ginger, but that alcohol is a much better solvent for this purpose.

Heydenreich, F. V.

1868

On Cubebin and the Diuretic Principle of Cubebs.

Am. Journ. Pharm., 40, p. 42.

Eighty ounces of cubebs yielded, when extracted with ether, 19 ounces of oleoresin or nearly 24 per cent.

The results obtained in the administration of cubebin, the volatile oil and the soft resin are given.



Rump, C.

1869

Extractum Lupulini aethereum.

Arch. d. Pharm., 189, p. 232. [Jahresb. d. Pharm., 4, p. 39.]

The extract of lupulin is directed to be prepared by macerating the fresh drug with ether, decanting and evaporating the ethereal solution to the consistence of a thin syrup.

Squibb, E.

1869

Report of the Committee on the Pharmacopœia.

Proc. A. Ph. A., 17, p. 298.

The process of repercolation is stated to be well adopted to the preparation of the oleoresins and that it materially lessens their cost.

Lefort, M. J.

1870

Mémoire sur les extraits sulfocarboniques, et sur leur emploi dans la préparation des huiles médicinales.

Journ. de Pharm., 90, pp. 102-110.

In considering the methods of medicating oils, the author proposes preparing the extract of the leaves of *Conium maculatum* by exhausting the drug with carbon disulphide and subsequently removing the solvent by evaporation.

Hager,

1871

Zur Bereitung des Extractum Filicis aethereum.

Pharm. Centralh., 12, p. 457. [Am. Journ. Pharm., 44, p. 164.]

It is stated that, if the rhizomes are dried over burned lime previous to extraction, and anhydrous ether (Sp. gr. below 0.723) used as the extracting solvent, the oleoresin does not deposit on standing but remains perfectly clear.

Maisch, J. M.

1872

On the use of Petroleum-Benzine in Making Oleoresins.

Am. Journ. Pharm. 44, p. 208. [Pharm. Journ., 31, p. 968; Proc. A. Ph. A., 21, p. 138; Year-Book of Pharm., 10, p. 328.]

Petroleum benzine, sp. gr. 0.700, is stated to have been used to advantage in the preparation of the oleoresins of capsicum, cubeb and ginger, but the author regards the use of this solvent in the place of ether as inadmissible until it has been proven that the proximate principles not extracted by the benzine are medicinally inert.

Buchheim

1873

Fructus Capsici.

Vierteljahresschr, f. prakt. Pharm., 22, p. 507.

[Proc. A. Ph. A., 22, p. 106.]

The *capsicin* sold by the firm of E. Merck is stated to be the ethereal extract of the capsicum fruit.

Remington, J. P.

1873

On the Use of Petroleum Benzin for Extracting Oleo-resinous Drugs.

Proc. A. Ph. A., 21, p. 592.

It is stated that benzin does not extract all of the diuretic principles from buchu and that its use for extracting the oleoresinous drugs is limited on account of its inflammability and great volatility.

Patterson, J.

1875

Aspidium marginale, Willdenow.

Am. Journ. Pharm., 47, p. 292.

The ethereal extract compared very favorably in appearance, taste and color with the best German oleoresin of male fern which could be obtained upon the market. An acid resembling the filicic acid of Luck was isolated therefrom.

Kruse

1876

Versuch einer vergleichenden Analyse der in den Monaten April, Juli und October 1874, in der Umgegend Wolmars gesammelten Radicis filicis maris.

Arch. d. Pharm., 209, p. 24.

The results obtained in the analyses of rhizomes gathered during the months of April, July and October are tabulated. The rhizomes gathered in April and October were found to have a more intensive green color and stronger odor than those gathered in July. The rhizomes gathered in April and July yielded a yellow colored extract while those gathered in October gave a beautiful green colored product.

Griffin, L. F.

1877

Preparations of Cubebs.

Am. Journ. Pharm., 49, p. 552.

The author found that cubebs yielded 16.5 per cent. of oil and resin to gasoline, while the wax and cubebin were not extracted. He, therefore, concludes that gasoline is adapted to the making of a good oleoresin of cubebs.

Wolff, L.

1877

On the use of Petroleum Benzin in Pharmacy.

Am. Journ. Pharm., 49, p. 1.

It is stated that benzin does not extract any of the pungent resins from ginger, no cubebic acid from cubebs, no piperin from pepper, and no santonin or resin from wormseed.

Cressler, C. H.

1878

On *Aspidium marginale*, Swartz.

Am. Journ. Pharm., 50, p. 290.

The author prepared an oleoresin from what he thought was male fern, but later proved to be *Aspidium marginale*. According to his report, it proved effective in expelling tapeworm.

Rohn, E.

1878

Recovering Ether in the Preparation of the Ethereal Extracts.

Schweiz. Worchenschr. f. Chem. u. Pharm., —, p. — [Year-Book Pharm., 16, p. 250.]

The author recommends mixing the exhausted drug with water and then heating the mixture over a direct flame up to 60° C, when the ether remaining in the marc distills over. In this manner three kilos of ether are stated to have been recovered from eight to ten kilos of male fern used in the preparation of the extract.

Kennedy,

1879

*Aspidium marginale*.

Am. Journ. Pharm., 51, p. 382.

Favorable results in the expulsion of taenia by the administration of oleoresin of *Aspidium marginale* are reported.

Thresh

1879

Proximate Analysis of the Rhizome (Dried and Decorticated) of Zingiber Officinalis and Comparative Examination of Typical Specimens of Commercial Gingers.

Pharm. Journ., 39, pp. 171 and 191.

The yield of ether extract is given as follows: Jamaica ginger, 3.29 per cent., Cochin, 4.965 per cent., African, 8.065 per cent. It is further stated that twice as much ether is required to exhaust the African ginger as it is necessary in the case of the other sorts (p. 191.)

- Bowman, J. 1881  
Aspidium rigidum.  
Am. Journ. Pharm., 53, p. 389. [Pharm. Journ. 12, p. 263.]

A crystalline substance thought to be identical with the *Filixsæure* of Luck was obtained from the ethereal extract of *Aspidium rigidum*.

- Seifert, O. 1881  
Einiges ueber Bandwurmkuren.  
Wien. Med. Wochenschr., 31, p. 1364. [Centralb. f. klin. Med. 3, p. 1884.]

The author contends that the extract should be prepared from the peeled fresh drug gathered in May or October as drying causes the loss of a greater part of the volatile oil. The ether should not be evaporated until just before the extract is to be dispensed.

- Maisch, J. M. 1883  
Comparison of Galenical Preparations of the United States and German Pharmacopœias.  
Am. Journ. Pharm., 55, p. 398.

In the preparation of oleoresin of cubebs, the German Pharmacopœia directs that a mixture of equal parts of ether and alcohol be used as a menstruum, while the *U. S. Pharmacopœia* directs that ether alone be used. In the preparation of oleoresin of aspidium, the solvents are the same (ether) but the German Pharmacopœia directs that the oleoresin be prepared by maceration instead of percolation as in the *U. S. Pharmacopœia*.

- Krämer 1884  
Extractum filicis maris.  
Pharm. Centralh., 25, p. 578.

The fresh rhizomes gathered in May or October, are directed to be extracted with ether containing a little alcohol. The tincture thus obtained is to be preserved in a cool place and the oleoresin prepared therefrom immediately before dispensing.

- Berenger-Feraud 1886  
Valeur taenifuge de la fougère de Normandy.  
Journ. de Pharm. et de Chim., 14, p. 321. [Arch. d. Pharm., 224, p. 134.]

The author states that the rhizomes gathered in Normandy have scarcely any action while those gathered in the Vosges or Jura mountains are very active as taenifuges.

- Jones, E. W. 1886  
 Amount of Starch in Ginger.  
 Chem. & Drugg., 28, p. 413. [Arch. d. Pharm., 224, p. 769.]  
 The yield of ethereal extract is given as 3.58 per cent., of alcoholic extract as 3.38 per cent.
- 
- Extractum Cubebarum aethereum. 1887  
 Gehe & Co. Handels -Ber. Sept., 1887, p. 50.  
 It is stated that, upon long standing, the extract of cubebs deposits a crystalline substance. The firm, therefore, cannot guarantee that the extract will remain clear.
- Kremel, A. 1887  
 Notizen zur Pruefung der Arzneimittel.  
 Pharm. Post, 20, p. 521. [Archiv. d. Pharm., 225, p. 880.]  
 Methods for the identification and evaluation of the ethereal extract of cubebs are presented. The chemical constants of both the alcoholic and ethereal extracts are tabulated (p. 522.) Analytical data on the alcoholic and ethereal extract of male fern are also given (p. 523.)
- Lippincott, C. P. 1887  
 What Are the uses of Benzine and the Lighter Petroleum Products in Pharmacy?  
 Proc. Penn. Pharm. Assoc., 10, p. 156.  
 The six official oleoresins were prepared using "benzole" as the exhausting menstruum.
- Keefer, C. D. 1888  
 Aspidium marginale, Willdenow.  
 Am. Journ. Pharm., 60, p. 230.  
 The author states that the ethereal extract of the rhizomes of *Aspidium marginale* contains 0.61 per cent. of resin, and chlorophyll. *Filicic acid* could not be identified.
- Siggnis, F. M. 1888  
 Comparative value of commercial gingers.  
 Am. Journ. Pharm., 60, p. 278.  
 The following percentages of resin were obtained on extracting ginger with alcohol, sp. gr. 0.820.
- |                           |      |           |
|---------------------------|------|-----------|
| Jamaica, unbleached ..... | 5.0  | per cent. |
| Jamaica, bleached .....   | 4.8  | " "       |
| East Indian .....         | 6.65 | " "       |
| East Indian .....         | 6.57 | " "       |
| African .....             | 6.17 | " "       |
| African .....             | 7.00 | " "       |

- Trimble, H. 1888  
The Comparative Extractive Powers of Ether and Benzin.  
Proc. Penn. Pharm. Assoc., 11, p. 60.

The following percentages of oleoresin were obtained on extraction with ether: aspidium, 6.51 per cent; capsicum, 19.5 per cent; cubebs, 21.26 per cent; lupulin, 60.59 per cent; pepper, 7.89 per cent. and ginger, 3.07 per cent. The same drugs yielded to benzin 5.9, 18.5, 16.65, 7.04, 2.8 and 2.48 per cent., respectively.

- Greenwalt, W. G. 1889  
Oleoresin of Male Fern.  
Am. Journ. Pharm., 61, p. 169. [Proc. A. Ph. A., 37, p. 379.]

The sediment deposited by the *etheral oil of male fern* was found by actual test to be as active as the supernatant oil; experiment is thus said to help out the statement (U. S. P. 1880) that the granular deposit should be thoroughly mixed with the liquid portion before being used.

- Minner, L. A. 1890  
Oleum Peponis.  
Am. Jour. Pharm., 62, p. 274. [Proc. A. Ph. A., 38, p. 323.]

The pumpkin seeds comminuted with pumice stone are directed to be extracted with ether. Such a preparation is stated to have proved to be an effective taenifuge, whereas *Oleum Peponis* was ineffective.

- Dieterich 1891  
Extracta.  
Helfenberger Ann., 1891, p. 29.

One sample of extract of male fern examined showed a "moisture content" of 2.7 per cent. and gave 0.40 per cent. of ash.

- Kuersten, R. 1891  
Ueber Rhizoma Pannae, *Aspidium athamanticum* Kunze.  
Arch. d. Pharm., 229, p. 258.

The author found no filix acid in the ethereal extract, but a substance *Pannasaeuere* having the formula  $C_{11}H_{14}O_4$ . A fatty and volatile oil were also isolated. The extract was found to be as active as the extract of male fern in the expulsion of tape worm.

Poulsson, E.

1891

Ueber den giftigen und bandwurmtreibenden Bestandtheil des aetherischen Filixextractes.

Arch. f. exper. Path. u. Pharm., 29, p. 1.

Filix acid is stated to occur in two forms, amorphous and crystalline. The first is reported to be therapeutically active, the latter is not. The crystalline acid is thought to be an anhydride or lactone of the amorphous acid. The author gives the name *Filicin* to the crystalline acid.

Rayman

1891

Wirkung des Extractum Filicis aethereum.

Pharm. Post, 24, p. 933.

It is stated that the extract of male fern is not well borne when taken internally if the ether has not been completely removed.

Reuter, Ludwig

1891

Ueber die Beziehungen des Filixsauregehaltes zur Wirkung des Extractum Filicis aethereum.

Pharm. Ztg., 36, p. 245. [Pharm. Post, 24, p. 511; Am. Journ. Pharm., 63, p. 288.]

It is stated that, in 14 out of 15 cases, prompt action was obtained using an extract which showed no deposit of filix acid and which left no residue of filix acid after treating with petroleum ether. On the other hand extracts which were rich in a deposit of filix acid also showed prompt action.

Professor Kobert is cited as stating that the Russian extract is about ten times as active as the German extract and twenty times as active as the French extract.

Riegel, S. J.

1891

Ginger and its Oleoresin.

Am. Journ. Pharm., 63, p. 531. [Year-Book of Pharm., 29, p. 168.]

Unbleached Jamaica ginger and East Indian ginger (having epidermis removed) yielded 5 and 8 per cent., respectively, of oleoresin to alcohol. The unbleached Jamaica ginger gave 2.5 per cent. of extractive matter to benzoin and the East Indian ginger gave 8 per cent. of oleoresin to ether. All of the foregoing oleoresins were found to be completely soluble in alcohol and chloroform.

1892

Extractum Alcanthae aethereum.

Gehe & Co., Handels-Ber. Apr. 1892, p. 46.

The ether extract of alkanet root is stated to be completely soluble in oil which is said not to be true of all commercial alkanet extracts.

Beringer, G. M.

1892

## Oleo-resins.

Am. Journ. Pharm., 64, p. 145. [Proc. A. Ph. A., 40, p. 474; Pharm. Centralh., 33, p. 314; Jahresb. d. Pharm., 27, p. 589.]

The author presents experimental data to show that acetone might be used to advantage in the preparation of the official oleo-resins. He especially recommends the use of this solvent in the preparation of the oleo-resin of ginger. The yield of oleo-resin, using acetone as the extracting solvent for the various drugs, is reported to be as follows: aspidium, 18 per cent; capsicum, 18 per cent. (25 per cent. when the drug was completely exhausted); cubebs, 21.75 to 25 per cent; lupulin, 71 per cent; pepper, 5.93 per cent; ginger, 5.57 per cent; and parsley seed 24 per cent.

Dieterich

1892

## Extracta spissa et sicca.

Helfenberger Ann., 1892, p. 44.

Three lots of extract of male fern gave 1.50, 2.10 and 1.50 per cent., respectively, of "moisture" and showed an ash content of 0.55, 0.55 and 0.55 per cent., respectively.

Kobert

1892

## Ueber die wirksamen Bestandtheile im Rhizoma Filicis maris.

Pharm. Post, 25, p. 1325. [Apoth.-Ztg., 8, p. 77; Chem. Centralb., 64, p. 269; Arch. d. Pharm., 231; p. 350, Pharm. Ztg., 38, p. 64.]

The author states that the volatile oil of male fern is therapeutically active and that Poulsson's statement based on the work of Carlbohm, Liebig and Rulle, that the activity is due to filix acid alone is erroneous. He cites as an example the activity of *Aspidium athamanticum* Kunze, which contains no traces of filix acid but contains the volatile oil.

Sherrad, C. C.

1892

## Value of Oleo-resinous Drugs.

Chem. and Drugg., 40, p. 523. [Year-Book Pharm., 29, p. 157.]

The yield of oleo-resin obtained using ether as a menstrum is reported to be as follows:

Capsicum, 4 samples, 15.5, 17.4, 18.3 and 18.4 per cent; cubebs, 9 samples, 16.4, 18.8, 21.06, 21.9, 23, 24.7, 24.8, and 24.8 per cent; ginger, 4 samples, 3.85, 4.72, 5.2, and 5.4 per cent; lupulin, 1 sample, 66.5 per cent; crude whole male fern rhizomes, 2 samples, 9.27 and 9.87 per cent; peeled male fern rhizomes, 3 samples, 7.1, 7.26 and 8.9 per cent.



Weppen and Lueders

1892

Ueber Extractum Filicis.

Apoth.-Ztg., 7, p. 514. [Pharm. Ztg., 38, 922; Pharm. Post, 25, p. 1173.]

It is stated that the extract prepared according to the *D. A. III* should have a yellowish-green color but not a deep green color. Preparations having a deep green color probably have chlorophyll or copper salts added to them. Copper can best be detected by dissolving the ash in hydrochloric acid and making the usual tests for the metal.

Two samples (commercial) of a deep green color were found to contain 0.056 and 0.044 per cent. of copper, respectively.

1893

Extractum Filicis aethereum.

Gehe &amp; Co., Handels-Ber., Apr., 1893, p. 43.

The condition of the season in which the rhizomes are harvested is stated to have a marked effect on the color of the extract. Sometimes the genuine extract is very dark green in color, especially in dry seasons.

Beckurts and Peters.

1893

Extractum Filicis.

Apoth.-Ztg., 8, p. 549.

Upon examination, two beautiful green samples of the commercial extract were found to contain 0.135 and 0.044 per cent. of copper, respectively, evidently added for the purpose of coloring the product. An extract prepared by the author was yellowish green in color and contained no copper. A warning is issued against the use of copper utensils in the preparation of the extract.

Dieterich

1893

Extracta spissa et sicca.

Helfenberger Ann., 1893, p. 38.

One sample of extract of cubeb showed a "moisture" content of 32.7 per cent. and gave 0.50 per cent of ash (p. 39).

Three samples of extract of male fern contained 1.15, 1.60 and 1.75 per cent. of "moisture" and gave 0.50, 0.50 and 0.50 per cent. of ash, respectively (p. 39).

Dyer and Gibbard

1893

Determination between Genuine and Exhausted Ginger.

Analyst, 18, p. 197. [Proc. A. Ph. A., 42, p. 936.]

The ether extract of genuine ginger is stated to be 3.0 to 5.2 per cent. After exhausting with ether, alcohol was found to yield 0.8 to 1.5 per cent. additional extractive matter.

Bedall 1894

Extractum Cubebæ Aethereum.

Pharm. Ztg., 39, p. 49.

The author states that the extracts having a green color give a more intensive reaction for cubeb than those having a brownish color. This does not apply when the green color is due to the presence of salts of copper.

Dieterich 1894

Extracta spissa et sicca.

Helfenberger Ann., 1894, p. 72.

Three samples of extract of male fern were found to contain 3.65, 2.32 and 1.90 per cent., respectively, of "moisture." The same samples gave 0.55, 0.42 and 0.50 per cent., respectively, of ash.

Emmanuel, L. 1894

Do Drugs Supplied by the Jobber Comply with Pharmacopœial Requisition. If Not, Who is Responsible, The Jobber or the Retailer?

Am. Journ., Pharm. 56, p. 358.

A sample of powdered cubebs obtained from an Eastern firm yielded 18 per cent. of a brown oleoresin. This was reported to the seller who replied: "the *U. S. Pharmacopœia* specifies the unripe fruit, but this is rarely found in the market, the regular article of commerce being the ripe fruit which contains less chlorophyll." p. 360.

Hell & Co.

Zur Kritik über Extract-Vorschriften und ueber fabrikmässig dargestellte Extracte.

Pharm. Post, 27, pp. 168-171. [Journ. de Pharm. et de Chim., 139, p. 493.]

Copper is stated to be a natural constituent of the male fern rhizome. Duplicate analyses of a sample of the rhizomes carefully powdered in an iron mortar, and incinerated in a porcelain dish showed 0.0144 and 0.0148 per cent. of copper, respectively. An ethereal extract prepared in the company's laboratory showed 0.033 per cent. of the metal and a commercial sample of the extract gave 1.96 per cent. Likewise, a commercial sample of extract of cubeb was found to contain 0.40 per cent. of copper.

Poulsson, E.

1894

Beitraege zur Toxicologie der Farnkräuter.  
Pharm. Post, 27, p. 238.

Two new acid substances  $C_{24}H_{40}O_{14}$  and  $C_{24}H_{40}O_{14}$  are reported to have been isolated from the rhizomes of *Polystichum spinulosum*. They were found to be toxic.

1895

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Extractum Orleanae aethereum.

Gehe & Co., Handels-Ber. Apr., 1895, p. 53.

It is stated that good "bixinreiche" orlean species are rare. The extract is said to be used for coloring "Genussmitteln."

1895

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Extractum Cubebæ aethereum liquidum.

Gehe & Co., Handels-Ber., Apr., 1895, p. 53.

A note concerning the precipitation of resin.

Bourquelot, Em.

1895

Réactions d'identité de quelques médicaments galéniques officinaux.

Journ. de Pharm. et de Chim., 140, p. 361.

The *Extrait de Cubebe* of the French Codex is semi-liquid, that of the German and Austrian pharmacopœias of the consistence of fresh honey. To identify the oleoresin, a small quantity is placed in a white porcelain dish and a few drops of concentrated sulphuric acid are added. The genuine oleoresin gives a purple-red color immediately.

Davis, R. G.

1895

Ginger.

Am. Journ. Pharm. 67, p. 597. [Proc. A. Ph. A., 44, p. 538.]

The yield of oleoresin obtained from ginger by the official process was found to be as follows:

Jamaica ginger, whole rhizome, bleached, 4.53 to 4.62 per cent; Jamaica ginger, whole rhizome, unbleached, 2.82 to 4.41 per cent; Jamaica ginger, powdered unbleached, 4.48 per cent; Races ginger, powered, bleached, 4.09 to 5.40 per cent; Races ginger, whole rhizome, bleached, 4.02 to 5.75 per cent; African ginger, whole rhizome, 5.75 per cent; African ginger, powdered, 6.27 per cent.

Dieterich 1895

*Extracta spissa et sicca.*

Helfenberger Ann., 1895, p. 17.

One sample of extract of cubebs contained 20.90 per cent. of "moisture" and showed an ash content of 0.47 per cent. (p. 17).

A sample of extract of male fern showed a "moisture" content of 1.75 per cent. and gave 0.50 per cent. of ash (p. 18.)

Hyers, P. 1895

*Fluid Extract of Cubeb.*

Am. Journ. Pharm., 67, p. 519.

The following percentages of oleoresin are reported to have been yielded by cubebs to different solvents: ether, 22.45 per cent; alcohol, 14.48 per cent; acetone, 18.48 per cent; petroleum ether, 13.47 per cent.

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1896

*Extractum Filicis Ph. G. III.*

Caesar and Loretz, Geschaeffts-Ber., Sept. 1896, p. 46.

The firm attributes the uniform activity of their extract of male fern to the fact that the rhizomes are obtained from the same locality each year, that they are collected in the autumn and, after carefully garbling, are immediately made into extract.

Fromme's method for estimating the filix acid content of the extract is given.

Alpers, W. C. 1896

*Oleoresin Capsicum.*

Merck's Rep. 5, p. 593.

The author states that he obtained a yield of 19 per cent. of oleoresin after removing the fat by filtration instead of 5 per cent. as usually given in the text-books.

Bocchi, I. 1896

*Methoden zur Feststellung der Identitaet und der Guete des aetherischen Filixextraktes.*

Boll. Chim. farm., 1896, p. 449. [Apoth-Ztg., 11, pp. 597 and 837; Pharm. Ztg., 41, p. 596.]

Reactions for the identification of filix acid, and a method for the evaluation of the extract of male fern are given.

Dacomo and Scoccianti

1896

Die Bestimmung des Gehaltes an Filixsaure im kaeuflichen Extractum Filicis.

Boll. Chim. farm., 5, p. 129. [Pharm., Ztg., 39, p. 280; Jahresb. d. Pharm., 31, p. 583; Apoth.-Ztg., 11, p. 174; Proc. A. Ph. A., 44, p. 433.]

The filix acid content of a number of samples of extract of male fern (self prepared and commercial) was found to vary from 11.86 to 42.53 per cent., when assayed according to the method devised by the authors. The average yield of extract obtained is given as 10 per cent.

The quantity and quality of the extract is stated to be influenced by the locality in which the rhizomes are grown, the moisture content of the drug when extracted, and the solvent. Ether, specific gravity, 0.720, is stated to be the most suitable menstruum for this purpose. Ether, specific gravity, 0.756, yielded 17 per cent. of a brownish colored extract of a tarry consistence. The presence of alcohol is said to retard the complete extraction of the filix acid.

Dieterich

1896

Extracta spissa et sicca.

Helfenberger Ann., 1896, p. 33.

One sample of extract of male fern contained 1.62 per cent. of "moisture" and gave 0.45 per cent. of ash.

Kraft, P.

1896

Ueber die Wertbestimmung von Extractum Filicis und eine neue Bestimmungsmethode der Filixsaure.

Schweiz. Wochenschr. f. Chem. u. Pharm., 34, p. 217. [Zeitschr. d. Allg. Oesterr. Apoth. Ver. 34, p. 798; Zeitschr. f. Anal. Chem., 39, p. 531.]

It is stated that the method of Dacomo and Scoccianti for the evaluation of the extract of male fern does not give the filix acid content but the total acid content. Extracts examined by the author's method gave from 0.4 to 10.0 per cent. of filix acid.

A new constituent which the author calls *Filixwachs* was isolated from the extract.

Liverseege

1896

The Effect of Solvents on the Analytical Character of Ginger.

Pharm. Journ., 57, p. 112. [Apoth.-Ztg., 11, p. 639.]

The ethereal extract of ginger is stated to amount to 5.5 per cent. The yield to methyl alcohol is given as 6.5 per cent.

1897

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**Extractum Filicis, Ph. G. III.**

Caesar and Loretz, *Geschaefte-Ber.*, Sept. 1897, p. 62.  
[*Pharm. Centralh.*, 38, p. 34.]

Investigations carried on by the firm showed that the best time for harvesting the rhizomes of male fern is from the middle of September to the end of October. Rhizomes collected in the spring yielded an extract low in filix acid content.

The consistence of the abstract is said to be dependent upon variations in the rhizomes, thus rhizomes rich in wax give an extract which is not fluid at ordinary temperatures.

Fromme's improved method for estimating the filix acid is given.

1897

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**Extractum Filicis aethereum, P G.. III.**

Gehe & Co., *Handels-Ber.*, Apr. 1897, p. 60.

The results obtained in the assay of male fern extracts by the methods of Dacomo and Scoccianti, Bocchi, and Fromme are tabulated.

Boehm, R.

1897

**Beitraege zur Kenntniss der Filixsauregruppe.**

*Archiv. f. exp. Path. u. Pharm.*, 38, p. 35.

In addition to the volatile oil, fixed oil and filix acid, Boehm isolated four acid substances from the extract of male fern, viz: aspidin ( $C_{22}H_{20}O_7$ ), flavaspidic acid ( $C_{22}H_{20}O_8$ ), albaspidin ( $C_{22}H_{20}O_7$ ) and aspidinol ( $C_{12}H_{16}O_4$ ).

Candussio

1897

**Ueber die Bereitung des Extractum Filicis aethereum.**

*Pharm. Post*, 30, p. 7.

The author is impressed with the low cost of the commercial extract of male fern as compared with the cost when prepared by the apothecary himself. The examination of a number of samples from the best German houses showed a low filix acid content when estimated according to the method of Dacomo and Scoccianti. They were all of a beautiful green color, however.

Dieterich

1897

**Extracta spissa et sicca.**

Helfenberger *Ann.*, 1897, p. 244. [*Apoth.-Ztg.*, 13, p. 788;  
*Pharm. Centralh.*, 39, p. 775.]

Two samples of extract of male fern, D. A. III, lost 4.5 and 4.72 per cent., respectively, on drying at 100°C; and gave 0.43 and 0.52 per cent. of ash, respectively.

Dieterich contends that a standard, which does not take into consideration

the volatile oil as well as the filix acid, is worthless, as the former is also active as a taenifuge. Old extracts which are inactive show the normal amount of filix acid. The diminution in activity is said to be due to the loss of the volatile oil by resinification and evaporation (p. 248.)

Dieterich

1897

Extractum Filicis aetherum, D. A. III.

Extractum Cubebarum aethereum.

Erstes Dezennium d. Helfenberger Ann., 1886–1895, p. 322.

Eighteen samples of extract of male fern examined during 10 years showed a loss upon drying at 100°C of from 0.60 to 9.73 per cent. The same samples showed an ash content varying from 0.40 to 0.63 per cent.

Four samples of ethereal extract of cubeb showed a loss upon drying at 100°C of 20.13 to 32.7 per cent., and gave 0.10 to 0.52 per cent. of ash.

Glass and Thresh

1897

Commercial Gingers and Essence of Ginger.

Pharm. Journ., 58, p. 245. [Am. Journ. Pharm., 69, p. 320.]

Jamaica ginger was found to yield 6.0 per cent of extractive matter to ether; Cochin, 4.33 per cent; African, 6.33 per cent.

Lauren, W.

1897

Extractum Filicis spinulosae.

Finska Laekaresaellsk. Handl., 1897, p. 9. [Pharm. Centralh., 39, p. 975.]

The ethereal extract prepared from the rhizomes of *Aspidium spinulosum* is stated to be as active a taeniafuge as that prepared from *Aspidium filix mas*.

Madsen, H. P.

1897

Meddelelser fra Vesterbro Apotheke Laboratorium.

Arch. f. Pharm. og Chem., 54, p. 269. [Jahresb. d. Pharm., 32, p. 591; Apoth.-Ztg., 12, p. 461.]

Extracts of male fern from Denmark, Germany, Bohemia, central Russia and Livonia were tested quantitatively for filix acid according to Fromme's method. Those from Bohemia and central Russia gave from 0.71 to 0.97 per cent. of filix acid; two samples from Germany gave 5.58 and 9.58 per cent., respectively; an extract from Wolmar in Livonia gave 13.07 per cent; the extracts from Denmark, with two exceptions (6.07 and 8.25 per cent.), gave below 2 per cent. (p. 277.)

1898

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**Extractum Filicis aetherum.**

Gehe & Co., Handels-Ber., 1898, p. 68. [Pharm. Centralh., 39, p. 298.]

In the analyses of 11 extracts obtained during different years, 6 were found to contain aspidin, 0.2 to 3.0 per cent., but no filix acid; 4 samples contained filix acid but no aspidin; 1 sample showed a trace of aspidin and a small quantity of filix acid.

1898

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**Zur Arzneiform und Werthbestimmung des Filixextracts.**  
Pharm. Centralh., 39, p. 873.

The dilution of the extract of male fern with castor oil to a definite filix acid content is discussed.

1898

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**Extractum Filicis, Ph. G. III.**

Caesar and Loretz, Geschaefte-Ber., Sept. 1898, p. 72.

A continuation of the firm's investigations concerning the influence of time of harvesting upon the quality of the male fern rhizomes has shown that they do not contain the maximum amount of active constituents until the month of August. They, therefore, conclude that the rhizomes should only be harvested in the months of August, September and October.

It is further reported that analyses of the extracts recently prepared show that the present year's (1898) crop of rhizomes is, on the whole, lower in crude filicin content than that of the preceding year (1897.)

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**Bellingrodt, Fr.**

1898

**Ueber Rhizoma und Extractum Filicis.**

Apoth.-Ztg., 13, p. 869.

The crude, and purified filicin content of 8 different extracts of male fern prepared by the author from rhizomes obtained from different sources are given. Similar data in the examination of 9 commercial extracts are also reported.

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**Dieterich, K.**

1898

**Zur Werthbestimmung und Arzneiform des Filixextraktes.**  
Apoth.-Ztg., 13, p. 788.

The addition of castor oil to the extract of male fern in sufficient quantity to bring the filix acid content to a definite standard is recommended.



Duesterbehn, F.

1898

Rhizoma und Extractum Filicis in therapeutischer, chemischer und toxicologischer Beziehung.

Apoth.-Ztg., 13, pp. 713, 720, 729 and 734.

The article is principally a review of the literature on the extract of male fern and its constituents.

Lefils

1898

Zur Herstellung von Filixextract.

Pharm. Centralh., 39, p. 901. [Zeitschr. d. oest. Apoth. Ver., 37, p. 167; Pharm. Ztg., 43, p. 939.]

The author advises the mixing of the powdered rhizomes with castor oil before preparing the extract as he is of the opinion that this procedure will retard the evaporation of the volatil oil and the precipitation of the crystalline filix acid.

Idris, T. H.

1898

Notes on Extract of Ginger.

Am. Journ. Pharm., 70, p. 466.

The alcoholic extract of ginger known as *gingerine* does not contain all of the aromatic principles of the rhizome, as most of the essential oil is lost on removing the alcohol upon evaporation. Acetone boiling at 58°C was found to be the most suitable solvent for extracting ginger. The acetone extract is a dark brown substance of treacly consistence, intensely pungent and at the same time possessing the full aroma of ginger, the quality of which largely depends on the variety of ginger used.

Miehle, Feodor

1898

Eine empfehlenswerte Form der Verordnung von Extractum Filicis.

Apoth.-Ztg., 13, 777. [Pharm. Centralh., 39, p. 873.]

The author recommends diluting the extract with castor oil in order to make a standard preparation containing a definite amount of filix acid. He advises the introduction of such a preparation into the D. A. IV, under the name *Extractum Filicis oleatum*.

Plzak, F.

1898

Extractum Filicis.

Pharm. Centralh., 39, p. 687. [Jahresb. d. Pharm., 33, p. 547.]

The author found 6.48 per cent of filix acid in the extract of male fern by the Kraft method, 6.0 per cent. by Fromme's old method and 5.2 per cent. by Fromme's improved method.

Winton, Ogden and Mitchell

1898

Capsicum.

Rep. of Conn. Agr. Exp. Sta. (1898), p. 200.

The amount of extractive matter obtained with ether from different samples of red peppers is given as follows: Chilli colorado, 15.81 per cent; peppers from Natal, 16.85 per cent; from Nepaul, 21.31 per cent; and from Zanzibar, 16.19 per cent.

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1899

Recently Introduced Remedies.

Am. Drugg. & Pharm. Rec., 34, p. 129.

It is stated that the *extract of Filix Spinulosa* is an ethereal extract of the rhizome of *Aspidium spinulosum* and that it has been recommended as a substitute for the preparation made from *Aspidium Filix-mas*.

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1899

Extractum Filicis, Ph. G. III.

Caesar and Loretz, Geschaefte-Ber., Sept. 1899, p. 73.

A table showing the crude filicin and filix acid content of extracts prepared from 15 of the better samples of male fern rhizomes obtained from different sources in Germany is given.

Results showing the difference in extractive power of ether, sp. gr. 0.720 and ether, sp. gr. 0.728 are also given.

Hausmann, A.

1899

Ueber Extractum Filicis aethereum.

Arch. d. Pharm., 237, p. 544.

The examination of 21 commercial extracts of male fern obtained from various sources showed that aspidin was a constituent of 4 of them. As aspidin is said to be found only in *Aspidium spinulosum*, the author infers that the rhizomes of this species have been used to adulterate the official drug.

A method for the detection of aspidin is given.

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1900

Extractum Filicis.

Caesar and Loretz, Geschaefte-Ber., Sept. 1900, p. 77.

A table showing the crude and purified filicin content of 12 samples of extract of male fern is given

Attention is also called to the greater tendency of the extract, prepared with ether, specific gravity 0.728, to deposit than that prepared with ether, specific gravity 0.720. The deposited material is reported to have been identified by Boehm as filix acid and a wax-like substance.

1900

**Extractum Filicis aethereum.**

Gehe &amp; Co., Handels-Ber., Apr. 1900, p. 63.

The constituents of the extracts of *Aspidium filix mas*, *A. filix femina* and *A. spinulosum* are discussed.

Maish, H. C. C.

1900

**Oleoresins. Economical preparation.**

P. C. P., Alumni Report, March, 1900, p. 49. [Proc. A. Ph. A., 48, p. 495.]

Maish advises the use of the Soxhlet extraction apparatus for preparing the oleoresins on a small scale.

Patch, E. L.

1900

Answers to queries issued by the Scientific Section of the American Pharmaceutical Association.

Proc. A. Ph. A., 48, p. 199.

The commercial oleoresins frequently show the presence of acetone, p. 205.

1901

**Extractum Filicis.**

Caesar and Loretz, Geschaefte-Ber., Sept. 1901, p. 68.

The crude and purified filicin contents of 8 batches of extract of male fern prepared during the year are presented in tabular form.

Bennet

1901

**Report on Commercial Ginger.**

Pharm. Journ., 66, p. 522.

The yield of extractive matter obtained on exhausting ginger with ether and alcohol is given as follows:

Per cent. of ether extract:

Jamaica ginger (whole), 2.57 to 6.41.

" " (ground), 2.97 to 4.6.

Per cent. of alcoholic extract after ether:

Jamaica ginger (whole), 3.09 to 5.16.

" " (ground), 3.01 to 4.16.

Per cent. of alcoholic extract.

Jamaica ginger (whole), 3.94 to 5.61.

" " (ground), 3.41 to 5.67.

Cochin " (whole), 4.91 to 6.74.

" " (ground), 5.41 to 6.51.

African " (whole), 5.41 to 6.61.

" " (ground), 5.14 to 6.47.

- Dieterich 1901  
Extracta spissa et sicca.  
Helfenberger Ann., 1901, p. 170.  
One sample of extract of male fern, *D. A. IV*, gave 5.23 per cent. of "moisture" and 0.32 per cent. of ash (p. 171).
- Matzdorff, M. 1901  
Wertbestimmung des Rhizoma Filicis.  
Apoth.-Ztg., 16, pp. 233, 256 and 273.  
The various constituents of the extract of male fern are discussed with respect to their therapeutic activity. Of these filix acid is thought to be the most important. Tables showing the crude filicin and filix acid content of ethereal fluid extracts prepared by ordinary percolation and by extraction with a Soxhlet's apparatus are given.
- Stoeder 1901  
Bestimmung der Filixsäure in Extractum Filicis.  
Pharm. Ztg., 46, p. 541.  
A method very similar in all respects to that of Fromme for the estimation of the filix acid in the extract of male fern is described.
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- 1902  
Oleoresin of Insect Powder.  
Southall Bros. & Barclay, Lab., Rep., 10, p. 20.  
This oleoresin is said to be extracted from the powdered drug and is offered for sale, in the crude form, as an extract, or precipitated, in the form of a coarse powder.  
It is said to be useful as a basis for nursery hair lotions, dusting powders and similar articles.
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- 1902  
Extractum Filicis.  
Caesar and Loretz, Geschaefts-Ber., Sept. 1902, p. 73.  
It is stated that the crude filicin contains the amorphous acid recently shown by Kraft to be the active principle of male fern extract. The estimation of the crude filicin will, therefore, be continued by the firm.
- Buttin, L. 1902  
Extract de Fougère mâle.  
Schweiz. Wochenschr. f. Chem. u. Pharm., 40, p. 234.  
A short review of the early work on the constituents of the extract of male fern is given.  
The variation in the constituents of the rhizomes due to the locality in

which they are grown, the time of the year when harvested, storing, etc., and the effect of the same upon the activity of the extract is emphasized.

Eight per cent of extract is reported as having been obtained from rhizomes harvested in the spring.

Kraft, F.

1902

#### Untersuchung des Extractum Filicis.

Schweiz. Wochenschr. f. Chem. u. Pharm., 40, p. 322.  
[Chem. Centralb., 73, 2, p. 53; Pharm. Ztg., 48, p. 275.]

Two new substances were isolated by the author from the ethereal extract of male fern, *flavaspidin* and an amorphous acid. The amorphous acid is reported to be the active principle and to be present to the extent of 5 per cent. in a good extract.

1903

Table showing suggested standards, ranges of specific gravity, etc., for galencial preparations.

Southall Bros., & Barclay, Lab. Rep., 11, p. 23.

The standard range for the specific gravity of *Extractum Filicis liquidum* is given as 1.000 to 1.019 at 15.5°C p. 24.)

1903

#### Extractum Filicis.

Caesar and Loretz, Geschaefts-Ber., Sept. 1903, p. 77.

It is reported that extracts prepared from the male fern rhizomes harvested during the previous year, when assayed according to the method of Kraft, yielded 27.08 to 36.6 per cent. of crude filicin.

1903

#### Ginger.

Southall Bros. & Barclay, Lab. Rep., 11, p. 13.

The following table shows the proportion of oleoresin found in three varieties of commercial ginger.

	Jamaica	Cochin	African
Per cent. sol. in alcohol (90 per cent.)	4.35	4.57	9.93
Per cent. sol. in ether, Sp. gr. 0.717	4.76	6.04	11.09

1903

#### Capsicum.

Southall Bros. & Barclay, Lab. Rep., 11, p. 13.

A sample of *Capsicum minimum* yielded 5.67 per cent. of material soluble in ether, Sp. gr. 0.717, and a sample of *Capsicum annum* yielded 15.34 per cent. to the same solvent.

Ballard

1903

Sur quelques condiments des colonies française (Anise étoilé, Cannelle, Cardamome, Curcuma, Gingembre, Girofle.

Journ. de Pharm. et de Chim., 157, pp. 248 and 296.

Ginger from the Ivory Coast is reported to have yielded 6.33 per cent. of ether extract, that from Tahiti, 3.75 per cent, p. 248.

Black pepper yielded the following percentages of extractive matter to ether: 10.15, 8.70 and 5.50.

Beythien

1903

Capsicum.

Zeitschr. Unters. Nahr. u. Genussm., 5, p. 858. [Pharm. Ztg., 47, p. 549; Proc. A. Ph. A., 51, p. 747.]

The examination of a number of commercial samples of powdered capsicum showed the following:

Yield of extract to ether (total)	12.54 to 19.70 per cent.
“ “ “ “ (av.)	14.94 “ “
“ “ “ “ alcohol (total)	26.55 to 35.71 “ “
“ “ “ “ (av.)	28.94 “ “

Dieterich

1903

Extracta spissa et sicca.

Helfenberger Ann., 1903, p. 240.

Three samples of extract of male fern examined showed a “moisture” content of from 5.52 to 7.38 per cent., and gave from 0.27 to 0.39 per cent. of ash (p. 241.)

Penndorff, O.

1903

Untersuchungen ueber die Beschaffenheit kaeuflicher Filix-Rhizoma und Extrakte.

Apoth.-Ztg., 18, p. 150.

The author states that the rhizomes turn brown on aging due to the breaking down of the *filix-tannic acid* into *filix-red* and sugar.

An examination of 20 samples of commercial rhizomes showed that 12 of them or over 50 per cent. contained rhizomes of *Aspidium spinulosum*, 1 sample consisted of 90 per cent. of this species.

Twenty samples of commercial extracts were examined with the following results:

4 samples—Starch present in small quantities.

1 sample—Aspidin present.

20 samples—6.65 to 18.31 per cent. crude filicin.

20 samples—1.06 to 7.48 per cent. filix acid.

20 samples—0.40 to 3.00 per cent. filix acid in solution.

20 samples—0.40 to 6.05 per cent. filix acid deposited.

7 samples—copper, more or less.

1904

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**Extractum Filicis.****Caesar and Loretz, Geschaefts-Ber., Sept. 1904, p. 77.**

It is stated that for years the firm has placed upon the market under their name an extract of male fern containing not less than 29 per cent. of crude filicin.

**Dieterich**

1904

**Ueber Extractum Filicis, D. A. IV.****Helfenberger Ann., 1904, p. 182.**

The results obtained in the examination of 3 samples of the extract of male fern are tabulated. The results include the per cent. of "moisture" and ash, and the iodine and saponification values.

1905

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**Extractum Filicis.****Caesar and Loretz, Geschaefts-Ber., Sept. 1905, p. 7.**

It is stated that, although the year's crop of male fern is poor, the firm guarantees a crude filicin content of 28 per cent. for their extract, (p. 71.)

Fromme's method for estimating the crude filicin content is given (p. 85.)

1905

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**Ueber die wirksamen Bestandtheile des Farnwurzel-extrakts. Pharm. Ztg., 50, p. 651.**

The work of Boehm, also that of Kraft, is commented on, special reference being made to *Filmaron* isolated from the extract by the latter.

1905

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**The Newer Remedies.****Am. Drugg. & Pharm. Rec., 46, p. 135.**

*Capsolin* which is recommended as a substitute for mustard papers, is said to consist of a mixture of oleoresin of capsicum, the oils of turpentine, cajuput and croton, with an ointment base. It is manufactured and marketed by Parke, Davis & Co., Detroit.

1905

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**The New U. S. P., Changes in Composition and Strength.  
Drug Topics, 20, p. 210. [Am. Journ. Pharm., 78, p. 412.]**

The new edition of the *U. S. P.* specifies acetone as the solvent for making all of the oleoresins with the exception of oleoresin of cubebs, which

is prepared with alcohol. It is stated that manufacturers have long since seen the folly of employing an expensive solvent like ether, and the adoption of acetone for this purpose is a recognition of commercial pharmaceutical advances. (p. 214.)

Dieterich 1905

*Extracta spissa et sicca.*

Helfenberger Ann., 1905, p. 159.

A sample of the ethereal extract of cubeb, *D. A. IV*, showed a "moisture" content of 55.91 per cent. and an ash content of 0.87 per cent. (p. 160.)

A sample of extract of male fern *D. A. IV*, gave a "moisture" content of 5.06 per cent., an ash content of 0.46 per cent. and yielded 23.22 per cent. of crude filicin (p. 161.)

Dieterich 1905

*Rhizoma Zingiberis.*

Helfenberger Ann., 1905, p. 131.

The following percentages of extract were obtained by exhausting ginger with different solvents, evaporating the latter and drying the residue at 100°C:

- 1) One part alcohol, 8 parts water — 7.86 per cent.
- 2) Sixty-eight per cent. alcohol — 4.88 per cent.
- 3) Ninety per cent. alcohol — 2.79 per cent.

Dieterich 1905

*Rhizoma Filicis.*

Helfenberger Ann., 1905, p. 130.

During the year, a number of lots of male fern rhizomes were examined. The air-dried rhizomes yielded 9.94 to 10.60 per cent. of ethereal extract. The rhizomes when dried at 100°C yielded as high as 11.20 per cent. to the same solvent.

Francis, J. M. 1905

*The New Pharmacopœia: A Detailed Commentary on the Eighth Revision of the U. S. P.*

Bull. of Pharm., 19, p. 317. [Am. Journ. Pharm., 78, p. 412.]

Under acetone, it is stated that oleoresins prepared with this solvent will separate in two layers on standing owing to the fact that this ketone possesses in a measure the combined solvent properties of both alcohol and ether.



Vanderkleed, C. E.

1905

Report of the Committee on Adulterations.

Proc. Penna. Pharm. Assoc., 28, p. 47.

Eight assays of capsicum gave 9.4 to 23.9 per cent. of oleoresin, the average being 18.13 per cent. The standard for a good drug is stated to be 15 per cent.

Vieth, H.

1905

Ueber die Beziehung zwischen chemischer Zusammensetzung und medizinischer Wirkung einiger Balsamika.

Verh. d. Ges. deutsch. Naturf. u. Aerzte, 2, p. 364. [Jahresber. d. Pharm., 66, p. 13.]

*Kubebenextrakt* is reported to consist of terpenes (65 per cent.), resin acids (10 per cent.), and resins (25 per cent.)

1906

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Apiolin

Merck's Ann. Rep., 20, p. 34.

*Apiolin* is the raw ethereal oil obtained from the seed of *Petroselinum sativum* or from *Apiol viride* by extraction with a suitable solvent. It is a yellow fluid, sp. gr. 1.25 to 1.135, boiling at 280 to 300°C.

1906

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Extractum Filicis.

Caesar and Loretz, *Geschaefte-Ber.*, Sept. 1906, pp. 82 and 99.

The firm reports that the crude filicin content of the extract obtained from the current year's crop of male fern averages 27 per cent. (p. 82).

Fromme's method for estimating the crude filicin is given (p. 99).

Naylor, A. H.

1906

Progress in pharmacopœias: drugs and their constituents.

Year-Book of Pharm., 43, p. 204.

It is stated that in the present state of our knowledge, neither Dacomo and Scoccianti's, Kraft's nor Stoeder's process for the quantitative estimation of filicic acid is a measure of the anthelmintic value of the extract of male fern.

Roeder, Ph.

1906

Rhizoma Filicis.

Jahresb. d. Pharm., 41, p. 46.

The author states that the rhizomes of *Aspidium filix mas* should give at most 3 per cent. of ash and should yield at least 8 per cent. of extractive matter to ether, allowing the latter to evaporate spontaneously and then heating for 2 hours at 95°C, cooling in a desiccator and weighing. Three samples of rhizomes gave 2.52 to 2.92 per cent. of ash, respectively, and 9.22 to 10.1 per cent. of ether-soluble extract.

Wollenweber, W.

1906

Ueber Filixgerbsaeure.

Arch. d. Pharm., 244, p. 466.

In connection with his work on the tannic acid in the male fern rhizomes, the author presents the results obtained in extracting the drug in a Soxhlet's apparatus with various solvents, ether, benzol, and petroleum ether. At the end of six hours, extraction was found to be practically complete in all cases. The yield obtained in each case is given as follows; ether, 10.0 per cent., benzol, 9.06 per cent., petroleum ether, 9.08 per cent.

Extraction with alcohol of varying strength yielded extractive matter in the following quantities: alcohol (90 per cent.), 20.0 per cent., alcohol (96 per cent.), 16.6 per cent.

The fixed oil content of the ethereal extract is stated to be 70 to 75 per cent.

1907

Cubebs.

Evans Sons Lescher &amp; Webb, Analyt. Notes, 1, p. 21.

The oleoresin extracted by ether from four samples of cubebs amounted to (1) 22.08, (2) 22.6, (3) 21.13 and (4) 22.8 per cent., respectively.

Blome, W. H.

1907

Cubeba.

Proc. Mich. Pharm. Assoc., 1907, p. 68. [Bull. Hygienic Lab., No. 63, p. 225.]

Five samples of cubeb are reported which assayed from 18.85 to 26.88 per cent. of oleoresin.

Van der Harst, J. C.

1907

Lupulin.

Pharm. Weekbl., 44, p. 1506. [Bull. Hygienic Lab., No. 63, p. 301.]

Two samples of lupulin were found to contain 52 and 65 per cent. of ether-soluble matter, respectively.

Patch, E. L.

1907

Report of Committee on Drug Market.

Proc. Am. Pharm. Assoc., 55, p. 314.

The samples of capsicum examined yielded from 16.2 to 26.5 per cent. of alcoholic extract (p. 324.)

Smith, O. W.

1907

Galenicals of the U. S. P. VIII.

Proc. Mo. Pharm. Assoc., 29, p. 132.

The author is of the opinion that the oleoresin of cubeb might well have been included in the class made with acetone, as the drug yields but little on subsequent extraction with alcohol. Alcohol on the other hand is open to the objection that its boiling point is so high that a considerable loss of volatile substances from the cubeb occurs when the solvent is evaporated (p. 134.)

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1908

Extractum Filicis.

Caesar and Loretz, Geschaefts-Ber., Sept. 1908, pp. 76 and 99.

It is stated that for years the firm has estimated the crude filicin content of the extract of male fern and marketed a standard product containing 28 per cent. of this constituent as required by the Swiss Pharmacopœia, VI, (p. 76.)

Fromme's method for estimating the crude filicin is given (p. 99.)

Dohme and Engelhardt

1908

Purity of some official and non-official drugs and chemicals.

Proc. Am. Pharm., Assoc., 56, p. 814.

A sample of lupulin yielding only 56 per cent. of ether-soluble matter is reported (p. 817.)

- Patch, E. L. 1908  
Report of Committee on Drug Market.  
Proc. Am. Pharm. Assoc., 56, p. 765.  
The different samples of capsicum examined yielded from 15 to 25.2 per cent. of alcoholic extract (p. 768.)
- Spaeth, Eduard 1908  
Die chemische und mikroskopische Untersuchung der Gewürze und deren Beurteilung.  
Pharm. Centralh., 49, p. 581.  
The paper discusses the characteristics of several commercial varieties of ginger and the composition of the drug. The quantity of material extracted by ether, alcohol, petroleum ether and methyl alcohol is given.
- Vanderkleed, C. E. 1908  
Report of Committee on Adulteration.  
Proc. Penna. Pharm. Assoc., 31, p. 65.  
Three samples of capsicum yielded from 11.59 to 18.35 per cent. of oleoresin; four samples of cubeba, 16.39 to 23.6 per cent; two samples of ginger, 5.58 to 9.55 per cent; three samples of male fern, 6.68 to 17.9 per cent., average 10.002 per cent. (p. 88.)
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- Pharmacy Committee's Report. 1909  
Chem. & Drugg., 74, p. 288.  
The Committee of Reference in Pharmacy asserts that cubeba should yield not less than 20 per cent. of oleoresin to ether, sp. gr. not over 0.720. (p. 292.)
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- Extractum Filicis. 1909  
Caesar and Loretz, Geschaefte-Ber. Sept. 1909, pp. 67 and 84.  
A crude filicin content of 28 per cent. is guaranteed by the firm for the new lot of extract of male fern (p. 67.)  
Fromme's method for the estimation of the crude filicin is given (p. 84.)
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- Apiol. 1909  
Evans Sons Lescher & Webb, Analyt. Notes, 4, p. 11.  
A sample of apiol of French manufacture examined by the firm is reported as having been liquid and green in color. It yielded 40 per cent. of

its bulk to steam distillation. It is, therefore, thought that the sample was prepared by the extraction of parsley fruits with a suitable light solvent.

Bernegau, L. H.

1909

Report of the Committee on Adulteration.

Proc. Penna. Pharm. Assoc., 32, p. 119.

Ten samples of lupulin examined yielded from 34 to 65.8 per cent. of ether-soluble matter (p. 125.)

Dohme and Engelhardt

1909

Purity of some official and non-official drugs and chemicals.

Proc. A. Ph. A., Assoc., 57, p. 713.

Three samples of lupulin examined were low in ether-soluble matter yielding but 47.50, and 43 per cent., respectively (p. 716.)

Dunn, J. A.

1909

Suggested Modifications of U. S. P. and N. F. Formulas.

Proc. A. Ph. A., 57, p. 942.

It is stated that the oleoresin of male fern prepared by the *U. S. P.* method, using acetone, contains so much undesirable extractive matter that it is necessary to purify it by dissolving in ether. It is suggested that it might be worth while to consider whether the *U. S. P.* should not go back to the use of ether (p. 949.)

Parson, W. A.

1909

Report of the Committee on Adulteration.

Proc. Penna. Pharm. Assoc., 32, p. 119.

Three samples of lupulin yielded 66.1 and 54 per cent. of ether-soluble matter, respectively (p. 125.)

Patch, E. L.

1909

Report of Committee on Drug Market.

Proc. A. Ph. A., 57, p. 721.

The alcoholic extract from specimens of ginger examined varied from 3.7 to 6.2 per cent. (p. 739.)

Vanderkeed, C. A.

1909

Report of the Committee on Adulteration.

Proc. Penna. Pharm., Assoc., 32, p. 119.

Samples of capsicum, cubebs, ginger, and male fern examined are reported to have yielded oleoresin as follows: five samples of capsicum, 14.34 to 17.95 per cent; four samples of cubebs, 16.49 to 24.34 per cent; sixteen samples of Jamaica ginger, 3.142 to 6.91 per cent; two samples of African ginger, 8.2 and 9.036 per cent; one sample of male fern, 10.33 per cent. (p. 129.)

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1910

Extractum Filicis.

Caesar and Loretz, Jahres-Ber., Sept. 1910, p. 90.

Fromme's method for the estimation of crude filicin is given.

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1910

Cubebs.

Southall Bros. & Barclay, Lab. Rep., 17, p. 11.

Eight samples of cubebs, when extracted with petroleum spirits, yielded from 3.88 to 18.08 per cent. of extractive matter. The same samples on subsequent extraction with alcohol (90 per cent.) yielded from 3.4 to 5.66 per cent. of extractive matter.

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1910

Capsicum.

Southall Bros. & Barclay, Lab. Rep., 17, p. 8.

Two samples of capsicum (*B. P. C.*) yielded 15.4 and 14.0 per cent., respectively, of extract to benzol.

Dohme and Engelhardt

1910

The new Hungarian Pharmacopœia.

Proc. Am. Pharm. Assoc., 58, p. 1168.

The extraction of male fern with ether, as directed in the *Ph. Hung. III*, instead of acetone as in the *U. S. P., VIII*, is thought to be desirable since the latter is liable to extract substances which might produce injurious after effects (p. 1179.)

It is further stated that the yield of ether extract as given in the Hungarian Pharmacopœia is 8 per cent. (p. 1184.)

Eldred, F. R.

1910

Some data obtained in the examination of official substances.  
Proc. A. Ph. A., 58, p. 889.

Forty-eight lots of capsicum were examined. The yield of ether-soluble oleoresin, when the latter was dried for one hour on a water bath, was found to vary from 11 to 26 per cent., the average 18 per cent. (p.891.)

Gane, E. H.

1910

Pharmacopoeial notes and comments.  
Drug Topics, 25, p. 212.

It is stated that a good sample of cubebs should yield 20 per cent. of ether-soluble extract.

Gane and Webster

1910

Pharmacopoeial notes and comments.  
Drug Topics, 25, p.

Aspidium is stated to be one of the most useful of drugs when carefully collected and preserved, but that much of the rhizome is inert and is obtained from any old species of fern. It is said to be falling into disuse on this account. It is thought that the observance of more care in the collection of the drug and the preparation of the oleoresin would restore its popularity as an anthelmintic.

La Wall, C. H.

1910

Some suggested standards and changes, for the U. S. P.  
Am. Journ. Pharm., 82, p. 21.

The author asserts that a test for capsicum should be included in the U. S. P. requirements for the oleoresin of ginger as many commercial samples used in making ginger ale extracts contain oleoresin of capsicum and these occasionally find their way into the pharmaceutical trade.

A method for the detection of capsicum in the oleoresin of ginger based on the neutralization of the pungent principle of the ginger with potassium hydroxide is described (p. 25.)

Vanderkleed, C. E.

1910

Report of the Committee on Adulterations.  
Proc. Penna. Pharm. Assoc., 33, p. 131.

Seven samples of capsicum yielded from 15.10 to 22.27 per cent. of oleoresin; one sample of African ginger 10.12 per cent; two samples of Jamaica ginger 5.636 and 6.316 per cent., respectively (p. 147.)

1911

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**Extractum Filicis.****Caesar and Loretz Jahres.-Ber., Aug. 1911, pp. 76 and 105.**

Regret is expressed in that the *Ph. Germ. V.* has not included an assay for oleoresin of aspidium. The crude filicin content is thought to be a satisfactory indication of the value of this preparation. A filicin content of 27 per cent. is guaranteed by the firm for the new lot of the extract prepared by them (p. 76.)

Fromme's method of estimating the crude filicin is given (p. 105.)

1911

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**Male fern extract.****Evans Sons Lescher & Webb, Analyt. Notes, 6, p. 48.**

Five samples of male fern extract were tested. Two were found to be adulterated with castor oil (55 to 70 per cent.)

The Kraft and the Swiss pharmacopœial methods for evaluating the extracts are discussed and the results obtained in each case, along with other physical and chemical constants, are tabulated.

1911

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**Cubebs.****Southall Bros. & Barclay Lab. Rep., 19, p. 9.**

Five samples of cubebs yielded from 4.66 to 8.78 per cent. of extract to petroleum spirit, the average being 6.95 per cent.

1911

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**Insect Powder.****Southall Bros. & Barclay, Lab. Rep., 19, p. 10.**

Two samples of insect powder yielded 8.28 and 7.57 per cent. of oleoresin when tested by Durant's method.

One sample of Japanese insect flowers yielded 13.98 per cent. of oleoresin of an orange brown color.

1911

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**Oil of male fern.****Brit. & Col. Drugg., 60, p. 388.**

In this article, it is stated that parcels of the extract of male fern are being condemned in London as they have been found to contain large quantities of castor oil.

Suspicion was first aroused through the low selling price of some



of the extracts. The adulterated extract was being sold for 4s per pound while reliable manufacturers would not quote prices below 5s 6d per pound.

1911

Ext. Filicis maris.

Chem. & Drugg., 79, p. 749 and 798.

This editorial commenting on Parry's observation, that extract of male fern is commonly adulterated with castor oil, calls attention to the tests given in the Netherlands and Swiss pharmacopœias.

Bernegau, L. H.

1911

Report of the Committee on Adulterations.

Proc. Penna. Pharm. Assoc. 34, p. 117.

Three lots of lupulin tested 58.9, 57.7 and 62.1 per cent. soluble in ether (p. 125.)

Beythien, Hemple & Others

1911

Kurze Mitteilungen aus der Praxis des Chemischen Untersuchungsamtes der Stadt Dresden.

Zeitschr. Unters. Nahr. u. Genussm., 21, p. 666.

A table is presented showing the ash content and extract content of a number of samples of ginger (p. 668.)

According to Reich the volatile ether extract content varied from 0.80 to 4.02 per cent., the non volatile from 1.66 to 6.93 per cent; the alcoholic extract from 1.33 to 4.08 per cent; the petroleum ether extract from 1.14 to 4.49 per cent; and the methyl alcohol extract from 4.40 to 12.53 per cent.

Deane, Harold

1911

Oleoresina Capsici, B. P. C.

Pharm. Journ., 87, p. 804.

The author criticises the British Pharmaceutical Codex with respect to the title *Oleoresina Capsici*. He is of the opinion that the preparation has no right to the name *oleoresin*, as it corresponds more closely to the product sold as *capsicin* or *soluble capsin* for the use of pill makers and mineral water manufacturers.

Francis, J. M.

1911

Report of the Committee on Adulterations.

Proc. Penna. Pharm. Assoc., 34, p. 117.

Only one of eight lots of lupulin examined failed to exceed the required 60 per cent. of ether-soluble matter (p. 125.)

Gluecksmann, G.

1911

Ueber eine neue Identitätsreaktion des Extractum Cubeborum.

Pharm. Praxis, 1911, p. 98. [Apoth.-Ztg., 27, p. 334.]

A test in which hydrochloric acid is used for producing a color reaction is described in detail.

Parry, E. J.

1911

Extract of male fern.

Pharm. Journ. 87, p. 778. [Chem. & Drugg., 79, p. 860; Am. Journ. Pharm., 84, p. 136; Apoth.-Ztg., 26, p. 1046.]

The author reports on the examination of commercial extracts of male fern and finds that the greater part are undoubtedly adulterated with from 30 to 60 per cent. of castor oil. The physical and chemical constants of the commercial samples and of genuine extracts are tabulated for comparison.

Pearson, W. A.

1911

Report of the Committee on Adulterations.

Proc. Penna. Pharm. Assoc., 34, p. 126. [Bull. A. Ph. A., 6, p. 346.]

The author reports that two lots of oleoresin of aspidium were rejected because they were not green in color.

Rosendahl, H. V.

1911

Fern rhizomes, yield of extract and relative activity of.

Year-Book of Pharm., 48, p. 286. [Apoth.-Ztg., 26, p. 588; Svensk. farmac. Tidsk., 1911, p. 85.]

The yield of ethereal extract obtained from various species of fern harvested during different months of the year was found to be as follows:

	May	August	October
	Per cent.	Per cent.	Per cent.
<i>Aspidium filix mas</i>	—	12.5	11.0
<i>Dryopteris spinulosa</i>	—	17.0	—
<i>Dryopteris dilatata</i>	10.0	—	—
<i>Pteris aquilina</i>	2.0	—	—
<i>Athyrium filix femina</i>	0.9	—	—
<i>Aspidium alpestre</i>	0.7	—	—

Two grams of the extract of *Dryopteris dilatata* are stated to be therapeutically equivalent to 8 to 10 grams of the extract of *Aspidium filix mas* or four grams of the extract of *Dryopteris spinulosa*.

Vanderkleed, C. E.

1911

Report of the Committee on Adulterations.

Proc. Penna. Pharm. Assoc., 34, p. 117.

Two samples of capsicum are reported to have yielded 14.7 to 17.93 per cent., respectively, of oleoresin; one sample of subeba, 22.14 per cent; eleven samples of African ginger, 7.128 to 9.484 per cent; and eight samples of Jamaica ginger, 3.4 to 6.6 per cent. (p. 132.)

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1912

Extractum Filicis.

Caesar and Loretz, Jahres-Ber., Sept. 1912, p. 128.

The firm's method for estimating the crude filicin is given.

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1912

Capsicine.

Evans Sons Lescher & Webb, Analyt. Notes, 7, p. 18.

Five samples of *capsicine* examined were all entirely soluble in 10 volumes of 90 per cent. alcohol.

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1912

Male fern extract.

Evans Sons Lescher & Webb, Analyt. Notes, 7, p. 51.

Sixteen samples of male fern extract examined in 1912 were free from castor oil and of satisfactory purity. They showed a refractive index of 1.507 to 1.509 at 15°C, and gave a filicin content of 22.9 to 26.3 per cent., when assayed according to the method given in the Swiss Pharmacopœia.

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1912

Capsicum.

Johnson & Johnson, Lab. Notes, 1912, p. 14.

The yield of ether extract obtained from capsicum is reported to have varied from 16 to 19 per cent.

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1912

Cheap extract of male fern found badly adulterated.

Merck's Report, 21, p. 29 [Apothecary, 24, p. 14.]

A sample of cheap extract of male fern examined by Merck was found to be adulterated with 25 per cent. of castor oil, and to contain only 8 per cent. of crude filicin.

1912

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**Male fern extract.****Southall Bros., & Barclay, Lab. Rep., 20, p. 15.**

The statement of Parry that much of the male fern extract is adulterated is confirmed. The physical and chemical constants obtained in the examination of six commercial extracts are tabulated.

**Dohme and Engelhardt**

1912

**Drug quality during the period 1906-1911.****Journ. A. Ph. A., 1, p. 99.**

It is stated that there was hardly any variation in the percentage of oleoresin in the samples of cubebs examined during the last six years, (p. 101.)

**Goris and Voisin**

1912

The determination of the ether extract of male fern, and the unification of the methods of analysis.

**Bull. Sci. Pharmacolog., 19, p. 705, [Pharm. Ztg., 58, p. 129; Journ. 90, p. 81; Year-Book of Pharm., 50, p. 337.]**

It is stated that the method of the Swiss Codex gives values for crude filicin which are about 30 per cent. too high owing to the solubility of the ether solution in the solution of barium hydroxide. If the ether be driven off by heating to 50°C before filtering, the results will be comparable with those obtained by the magnesia methods.

**Hooper, D.**

1912

**Notes on Indian drugs.****Pharm. Journ. 89, p. 391.**

The examination of the rhizomes of Indian ginger, with reference to determining the relationship between maturity and oleoresin content, showed that young rhizomes develop oleoresin as they are allowed to grow. Those gathered in December yielded 6.4 per cent. of extract to alcohol (90 per cent.), while those gathered in February gave 8.3 per cent. Upon washing the extracts with water, the remaining insoluble residue amounted to 3.0 per cent. and 3.5 per cent., respectively. Some of the more mature rhizomes gave as high as 11.8 per cent. of alcoholic extract or 8.1 per cent. of washed resin.

**Patch, E. L.**

1912

**Report of the Committee on Drug Market.****Journ. A. Ph. A., 1, p. 499.**

Eight samples of Jamaica ginger gave from 3.3 to 6.0 per cent. of alcoholic extract (p. 500.)

Vanderkleed, C. E.

1912

Report of Committee on Drug Market.

Proc. Penna. Pharm. Assoc., 35, p. 165.

The assay of 4 samples of capsicum showed the oleoresin content to be from 14.41 to 16.7 per cent; five samples of cubebs yielded 1.735 to 24.49 per cent. of oleoresin; seventeen samples of Jamaica ginger, 3.444 to 6.640 per cent; ten samples of African ginger, 6.85 to 11.10 per cent (p. 179.)

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1913

Miscellaneous Inquiries.

Chem. & Drugg., 82, p. 470.

*Gingerin* is stated to be the extract obtained upon evaporating the tincture of ginger. It is said to vary with the variety of ginger used in the preparation of the tincture.

*Capsicin* is stated to be commercially indefinite. It may be a strong alcoholic extract, an ethereal, a chloroformic or an acetone preparation. The accepted *capsicin* of commerce, however, is the oleoresin prepared with ether.

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1913

Die Methoden zur Wertbestimmung des Filixextrakts.

Pharm. Ztg., 58, p. 129.

The methods of Goris and Voisin, and E. Schmidt for the evaluation of the extract of male fern are discussed.

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1913

Extractum Filicis.

Caesar and Loretz, Jahres.-Ber., Sept. 1913, pp. 98 and 106.

Four samples of extract of male fern prepared by the firm showed a crude filicin content of 32.64, 23.7, 28.15 and 30.4 per cent., respectively, (p. 98.)

The firm guarantees the filicin content of their extract to be 27 per cent.

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1913

Male fern extract.

Evans Sons Lescher & Webb, Analyt. Notes, 8, p. 44. [Year-Book of Pharm., 51, p. 244.]

Seven samples of extract of male fern examined during the year showed a filicin content of 21.3 to 25.3 per cent. and a refractive index of 1.5 to 1.51.

Three samples were impure or suspicious. They showed a refractive index of 1.495, 1.497 and 1.499, and a filicin content of 15.6, 19.6 and 19.7 per cent., respectively.

1913

Male fern extract.

Southall Bros., & Barclay, Lab. Rep., 21, p. 14.

The analytical data obtained in the examination of two commercial samples of the extract of male fern are given.

Bohrisch, P.

1913

Ueber Extractum Filicis.

Pharm. Ztg., 58, p. 601. [Chem. Abs. 8, p. 206.]

A comprehensive review of the constituents and the methods of evaluating the extract of male fern is given.

Four samples of commercial extracts in bulk were examined for density and crude filicin content. The findings for density were 0.9888, 0.9842, 0.9836 and 1.0109; for crude filicin 14.85; 15.42, 16.00 and 24.00 per cent. The same tests for five samples of the extract in capsules showed: density, 0.9824, not determined, 1.0135, 1.0255 and 0.9910; crude filicin, 15.02, 23.42, 26.77, 27.72 and 14.45 per cent.

Dohme and Engelhardt

1913

Cubebs.

Oil, Paint and Drug Rep., 83, p. 55.

The quantities of oleoresin obtained from cubebs ranged between 16 and 22 per cent.

DuMez, A. G.

1913

The physical and chemical properties of the oleoresin of Aspidium with respect to the detection of adulterations.

Philippine Journ. of Sc., 8, Sec. B., p. 523.

The methods of adulterating the oleoresin are discussed in detail. The physical and chemical constants of samples prepared in the laboratory and those obtained from various commercial sources are presented with the idea of indicating to what extent they may be relied upon in detecting a deteriorated or adulterated product.

Engelhardt, H.

1913

Purity of chemicals and drugs.

Journ. A. Ph. A., 2, p. 163.

Four samples of black pepper are reported to have yielded 10.6, 12.5, 9.2 and 11 per cent., respectively, of oleoresin; six samples of capsicum, 13.1, 41.8, 15.26, 15.8, 11.3 and 11 per cent; cubebs from 18 to 25 per cent; Jamaica ginger from 2.81 to 5.24 per cent; lupulin, eight samples out of twelve, less than 60 per cent; three samples of parsley seed. 14.7, 11.4 and 13.04 per cent. (pp. 164 and 165.)

- Gane, E. H. 1913  
Report of Committee on Drug Market, August, 1912.  
Journ. A. Ph. A., 2, p. 677.  
Four lots of lupulin gave 44.94 to 65.5 per cent. of ether-soluble material, (p. 681.)
- Harrison and Self. 1913  
Analytical constants of extract of male fern.  
Chem. & Drugg. 83, p. 182. [Year-Book of Pharm., 50, p. 494; Pharm. Journ. 91, p. 128; Pharm. Ztg., 58, p. 643.]  
The analytical constants of genuine and commercial extracts of male fern are tabulated. The authors do not approve of the standards suggested by Parry.
- Hill, C. A. 1913  
Analytical notes on extract of male fern.  
Chem. & Drugg., 83, p. 181. [Pharm. Ztg., 58, p. 643.]  
The analytical constants of 23 samples of extract of male fern are discussed and tabulated. The chemical and physical constants of the oily portion are also given for comparison with those of castor oil. One commercial sample is reported to have contained 59 per cent. of the latter.
- Osborne, Oliver F. 1913  
A last plea for a useful Pharmacopoeia.  
Journ. Am. Med. Assoc., 60, p. 1427.  
Among the "useless" preparations adopted by the Committee of Revision, the author includes the oleoresins of lupulin and parsley seed. (p. 1429.)
- Parry, E. J. 1913  
Extract of male fern.  
Chem. & Drugg., 83, p. 231.  
The author confirms the results which he published in an earlier paper.
- Patch, E. L. 1913  
. Report of the Committee on Drug Market.  
Journ. A. Ph. A., 2, p. 1081.  
The percentage of alcoholic extract obtained from the drugs tested is reported as follows:

Capsicum, four samples, 19 to 24 per cent; ginger, nine samples, 5.2, 5.7, 4.2, 4.0, 4.5, 4.9, 3.5, 4.8 and 4.3 per cent. pp. 1088 and 1094.

The yield of ether extract reported by Kebler is as follows:

Fifty-three samples, lupulin, 63.96 to 77.82 per cent; black pepper three lots, 10.04, 10.87 and 12.88 per cent; red pepper, eight samples, 13.0, 10.6, 14.7, 18.91, 13.12, 10.4, 13.25 and 14.7 per cent. The iodine values for the same were 132, 138, 123.4, 107, 127.3, 25.2 and 137.3. Seventeen other samples yielded from 11.22 to 20.77 per cent. The iodine value of these varied from 110 to 145.7 (pp. 1098 and 1101.)

Umney, J. C.

1913

What is capsicin?

Pharm. Journ., 91, p. 594.

Capsicin is stated to be a synonym for *Oleo-Resin of Capsicum* of the *B. P. Codex*, and, is made by extracting capsicum with 60 per cent. alcohol and subsequently evaporating off the solvent. It should not be confused with the preparations made with strong alcohol (90 per cent.), ether or acetone.

Vanderkleed, C. E.

1913

Report of the Committee on Drug Market.

Proc. Penna. Pharm. Assoc., 36, p. 77.

Thirty-seven samples of Jamaica ginger are reported to have yielded 3.10 to 5.75 per cent. of oleoresin; seventeen samples of African ginger, 6.85 to 9.92 per cent; seven samples of capsicum, 13.1 to 18.1 per cent; one sample of cubebs, 21.8 per cent.

Yagi, S.

1913

Physiologische Wertbestimmung von Filixsubstanzen und Filixextrakten.

Zeitschr. f. d. ges. exp. Med., 3, p. 64. [Therap. Monatsch., 1914, p. 443; Apoth-Ztg., 29, p. 544.]

A method in which earth worms are used for the purpose of testing the relative activity of extract of male fern and its constituents is described.

1914

Untersuchung der officinellen vegetabilischen Drogen.

Riedel's Ber. 58, p. 29.

The samples of cubebs examined are reported as having yielded 11.1 to 14.7 per cent. of extract soluble in ether 1 part and alcohol 1 part (p. 31.)

The alcohol extract obtained from capsicum varied from 31.9 to 35.3 per cent. (p. 32.)

The samples of aspidium examined gave 9.4 to 9.7 per cent. of ether-soluble extract.



1914

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Ueber Gelatinkapsel-Fabrikate.

Riedel's Ber. 58, p. 45. [Apoth.-Ztg., 29, p. 310.]

Capsules from only two manufacturers contained extract of male fern of which the crude filicin content was higher than 20 per cent. The extract of male fern in capsules from four other sources showed a filicin content of from 8.57 to 16.02 per cent. (p. 48.)

1914

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Extractum Filicis.

Caesar and Loretz, Jahres-Ber., Oct., pp. 23, 37, and 96.

The method of S. Yagi for the physiological standardization of the extract of male fern is stated to be too cumbersome for practical use. (p. 23.)

Extracts prepared in the laboratory showed the following crude filicin content, 25.48, 24.85, 29.7, 26.04, 26.0, 35.58, 27.35 and 33.79 per cent. (p. 37.)

It is further stated that the yield of ether extract, after evaporating on a water bath at 60°C to constant weight and drying in a desiccator for half an hour, should be about 15 to 18 per cent. (p. 96.)

1914

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United States Pharmacopœia Ninth Revision. Abstracts of proposed changes with new standards and descriptions.

Journ. A. Ph. A., 3, pp. 524 and 1573. [Year-Book of Pharm., 52, p. 324.]

It is stated that the former solvent, acetone, is to be changed to ether in the following: *Oleoresina Aspidii*, *Oleoresina Capsici*, *Oleoresina Zingiberis* and *Oleoresina Piperis*. (p. 551.)

Directions are also given for the preparation of *Oleoresina Petroselinii* (p. 573.)

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Bohrisch, P.

1914

Ueber verschiedene verbesserungbeduerftige Artikel des Deutschen Arzneibuches V.

Apoth.-Ztg., 29, p. 901.

It is stated that a large portion of the extract of male fern made in Germany shows a crude filicin content of less than 15 per cent., while the Swiss Pharmacopœia requires a content of 26 to 28 per cent. The author, therefore, thinks it desirable that a method for the estimation of the crude filicin in this preparation be given in the German Pharmacopœia.

E'we, G. E.

1914

Report of Committee on Drug Market.

Proc. Penna. Pharm. Assoc., 37, p. 125.

The author reports as follows on the oleoresins examined:

Four samples of oleoresin of capsicum were found to be pungent in dilutions of 1 to 150,000, the arbitrary standard of H. K. Mulford Company.

Seven samples of oleoresin of ginger were pungent to the taste in dilutions of 1 to 20,000, the arbitrary standard of H. K. Mulford Company.

One lot of oleoresin of cubeb contained the waxy deposit which the U. S. P. directs should be rejected.

One lot of oleoresin of say palmetto, "U. S. P." contained 15 per cent. of water which separated on standing. It also contained a large amount of insoluble matter (p. 152.)

Linke, H.

1914

Ergebnisse, Beobachtungen und Betrachtungen bei der Untersuchung unserer Arzneimittel.

Apoth.-Ztg., 30, pp. 606 and 628.

The results obtained in the examination of extract of male fern, in bulk and in capsules, obtained from various sources are tabulated. Especially the extract marketed in capsules was found to be low in filicin content.

Patch, E. L.

1914

Report of Committee on Quality of Medicinal Products.

Journ. A. Ph. A., 3, p. 1283.

A sample of oleoresin of capsicum examined is reported as having been found to be insoluble in ether, only slightly soluble in alcohol and almost completely soluble in water (p. 1298.)

Rippetoe, J. R.

1914

The examination of some drugs with special reference to the anhydrous alcohol and ether extracts, and ash.

Am. Journ. Pharm., 86, p. 435.

Four samples of capsicum are reported as having yielded 17.02 to 24.46 per cent. of extract to alcohol, and 16.49 to 17.88 per cent to ether, (p. 437.)

Six samples of cubeb gave 8.87 to 11.04 per cent. of alcoholic extract, and 7.68 to 9.80 per cent. of ethereal extract, (p. 438.)

Two samples of Jamaica ginger yielded 4.98 to 5.5 per cent. of extractive matter to alcohol, and 2.79 to 4.97 per cent. to ether. Two samples of African ginger yielded 6.20 to 6.23 per cent. to alcohol, and 5.3 to 5.45 per cent. to ether, (p. 439.)

Three samples of lupulin yielded 32.49, 55.18 and 57.06 per cent., respectively, of ethereal extract, (p. 440.)

Scoville, W. L.

1914

Report of Committee on Quality of Medicinal Products.  
Journ. A. Ph. A., 3, p. 1283.

It is stated that the samples of cubebs examined during the year gave from 18.1 to 22 per cent. of oleoresin, (p. 1287.)

Vanderkleed, C. E.

1914

Report of Committees on Drug Market.  
Proc. Penna. Pharm. Assoc., 37, p. 125.

On page 160, analytical data obtained from the laboratory of H. K. Mulford Company are reported showing the following yield of oleoresin for capsicum, cubebs and ginger:

	Lowest Yield. Per cent.	Highest Yield Per cent.	Average. Per cent
Capsicum (15 samples)	13.0	18.0	16.0
Cubebs (6 samples)	13.9	19.8	16.9
African ginger (3 samples)	8.50	9.61	9.0
Jamaica ginger (3 samples)	4.33	5.75	5.06
Male fern (4 samples)	6.85	10.12	8.23

1915

Male fern extract.

Southall Bros. & Barclay, Ann. Rep., 22 and 23, p. 17.

The filicin content of five samples of extract of male fern examined is reported as having varied from, 20.4 to 27.7 per cent., the specific gravity from 0.9885 to 1.030.

Glickman, L. H.

1915

Report of Committee on Drug Market.  
Proc. Penna. Pharm. Assoc., 38, p. 138.

Ten lots of lupulin examined are reported to have yielded the following percentages of ether-soluble matter: 55.5, 55.0, 57.1, 58.6, 54.7, 55.3, 44.2, 69.2, and 68.2, (p. 149.)

Vanderkleed, C. E.

1915

Report of Committee on Drug Market.  
Proc. Penna. Pharm. Assoc., 38, p. 138.

On page 155, the following data concerning the yield of oleoresin are

reported as having been obtained from the analytical laboratory of H. K. Mulford Company.

	Lowest Yield. Per cent.	Highest Yield. Per cent.	Average. Per cent.
Capsicum (6 samples)	13.85	20.84	16.65
African ginger (2 samples)	7.99	8.90	8.44
Jamaica ginger (1 sample)	3.93	3.93	3.93

Beringer, G. M.

1916

The reasons for some of the changes in the formulas of galenicals made in the ninth revision of the United States Pharmacopœia.

Journ. A. Ph. A., vol. 5, No. 12, p. 1390.

It is stated that acetone was the menstruum directed to be used in the preparation of the oleoresins by U. S. P., eighth revision, on account of cheapness. It is further stated that, since permission has been obtained to use denatured alcohol in the manufacture of ether, the cost of the latter has been reduced to such an extent that it has again become advantageous to use it in place of acetone. Hence, its use in the new Pharmacopœia.

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- 1887. Gehe & Co.
- 1888. Trimble, H.
- 1892. Sherrard, C. C.
- 1893. Dieterich
- 1894. Bedall
- 1894. Hell & Co.
- 1895. Hyers, P.
- 1895. Dieterich
- 1895. Gehe & Co.
- 1905. Vieth, R.
- 1905. Dieterich

*Oleoresin of Cubeb.*—Con.

- 1907. Blome, W. H.
- 1907. Smith, A. W.
- 1907. Evans Sons Lescher & Webb
- 1908. Vanderkleed, C. E.
- 1909. Vanderkleed, C. E.
- 1909. Chem. & Drugg.
- 1910. Gane, E. H.
- 1910. Vanderkleed, C. E.
- 1910. Southall Bros. & Barclay
- 1911. Southall Bros. & Barclay
- 1911. Vanderkleed, C. E.
- 1912. Dohme & Engelhardt
- 1912. Gluecksmann, G.
- 1912. Vanderkleed, C. E.
- 1913. Dohme & Engelhardt
- 1913. Vanderkleed, C. E.
- 1914. Maines and Gardner
- 1914. Rippetoe, J. R.
- 1914. Scoville, W. L.
- 1914. Vanderkleed, C. E.
- 1914. Journ. A. Ph. A.
- 1914. Riedel's Ber.

*Oleoresin of Ginger*

- 1834. Béal
- 1849. Procter, Wm., Jr.
- 1859. Procter, Wm., Jr.
- 1866. Rittenhouse, H. N.
- 1867. Pile
- 1872. Maish, J. M.
- 1877. Wolff, L.
- 1879. Thresh
- 1886. Jones, E. W.
- 1888. Trimble, H.
- 1891. Riegel, S. J.
- 1892. Sherrard, C. C.
- 1893. Dyer and Gilbard
- 1895. Davis, R. G.
- 1896. Liverseege
- 1897. Glass and Thresh
- 1901. Bennet
- 1903. Ballard
- 1903. Southall Bros. & Barclay
- 1905. Helfenberger Ann.
- 1908. Spaeth, Eduard
- 1908. Vanderkleed, C. E.
- 1909. Patch, E. L.

*Oleoresin of Ginger.—Con.*

- 1909. Vanderkleed, C. E.
- 1910. La Wall, C. H.
- 1910. Vanderkleed, C. E.
- 1911. Beythien, Hemple & Others
- 1911. Vanderkleed, C. E.
- 1912. Hooper, D.
- 1912. Patch, E. L.
- 1912. Vanderkleed, C. E.
- 1913. Engelhardt, H.
- 1913. Patch, E. L.
- 1913. Vanderkleed, C. E.
- 1913. Chem. & Drugg.
- 1914. Rippetoe, J. R.
- 1914. Vanderkleed, C. E.
- 1914. Journ. A. Ph. A.
- 1915. Vanderkleed, C. E.

*Oleoresin of Lupulin*

- 1823. Planche
- 1853. Livermore
- 1859. Procter, Wm. Jr.
- 1869. Rump, C.
- 1888. Trimble, H.
- 1892. Sherrard, C. C.
- 1907. Van der Harst, J. C.
- 1908. Dohme & Engelhardt
- 1909. Bernegau, L. H.
- 1909. Dohme & Engelhardt
- 1909. Parson, W. A.
- 1911. Bernegau, L. H.
- 1911. Francis, J. H.
- 1913. Gane, E. H.
- 1913. Engelhardt, H.
- 1913. Osborne, O. F.
- 1913. Patch, E. L.
- 1914. Rippetoe, J. R.
- 1915. Glickman, L. H.

*Oleoresin of Parsley Fruit*

- 1877. Wolff, L.
- 1892. Beringer, G. M.
- 1906. Merck's Ann. Rep.
- 1909. Evans Sons, Lescher & Webb
- 1913. Engelhardt, H.
- 1913. Osborne, O. F.
- 1914. Journ. A. Ph. A.

*Oleoresin of Pepper*

- 1825. Meli
- 1829. Carpenter, G. W.
- 1859. Procter, Wm. Jr.
- 1877. Wolff, L.
- 1888. Trimble, H.
- 1892. Sherrard, C. C.
- 1903. Ballard
- 1913. La Wall, C. H.
- 1913. Engelhardt, H.
- 1913. Patch, E. L.
- 1914. Journ. A. Ph. A.

*Oleoresin of Alkanet Root*

- 1892. Gehe & Co.

*Oleoresin of Annatto*

- 1895. Gehe & Co.

*Oleoresin of Cardamom Seed*

- 1849. Procter, Wm., Jr.
- 1859. " " "

*Oleoresin of Chenopodium*

- 1849. Procter, Wm., Jr.
- 1877. Wolff, L.

*Oleoresin of Clove*

- 1849. Procter, Wm., Jr.

*Oleoresin of Conium Leaves*

- 1870. Lefort, M. J.

*Oleoresin of Pepo*

- 1890. Minner, L. A.

*Oleoresin of Pyrethrum*

- 1849. Procter, Wm., Jr.
- 1859. " " "
- 1902. Southall Bros. and Barclay
- 1911. " " " "

*Oleoresin of Santonica*

- 1830. Schuppmann
- 1849. Procter, Wm., Jr.
- 1877. Wolff, L.



*Oleoresin of Savine*

1849. Procter, Wm., Jr.

*Oleoresin of Saw Palmetto*

1914. E'we, G. E.

*Oleoresin of Xanthozylum*

1849. Procter, Wm., Jr.

*Oleoresins (General)*

1869. Squibb, E.

1873. Remington, J. P.

1887. Lippincott, C. P.

1900. Maish, H. C.

1905. Francis, J. M.

1905. Drug Topics

1916. Beringer, G. M.







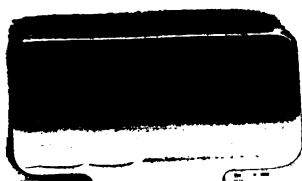
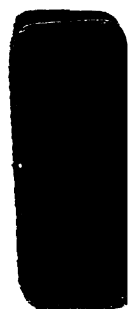




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